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Review

Thyroid hormones states and brain development interactions

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Abstract

The action of thyroid hormones (THs) in the brain is strictly regulated, since these hormones play a crucial role in the development and physiological functioning of the central nervous system (CNS). Disorders of the thyroid gland are among the most common endocrine maladies. Therefore, the objective of this study was to identify in broad terms the interactions between thyroid hormone states or actions and brain development. THs regulate the neuronal cytoarchitecture, neuronal growth and synaptogenesis, and their receptors are widely distributed in the CNS. Any deficiency or increase of them (hypo- or hyperthyroidism) during these periods may result in an irreversible impairment, morphological and cytoarchitecture abnormalities, disorganization, maldevelopment and physical retardation. This includes abnormal neuronal proliferation, migration, decreased dendritic densities and dendritic arborizations. This drastic effect may be responsible for the loss of neurons vital functions and may lead, in turn, to the biochemical dysfunctions. This could explain the physiological and behavioral changes observed in the animals or human during thyroid dysfunction. It can be hypothesized that the sensitive to the thyroid hormones is not only remarked in the neonatal period but also prior to birth, and THs change during the development may lead to the brain damage if not corrected shortly after the birth. Thus, the hypothesis that neurodevelopmental abnormalities might be related to the thyroid hormones is plausible. Taken together, the alterations of neurotransmitters and disturbance in the GABA, adenosine and pro/antioxidant systems in CNS due to the thyroid dysfunction may retard the neurogenesis and CNS growth and the reverse is true. In general, THs disorder during early life may lead to distortions rather than synchronized

Abbreviations: TPA, 12-*O*-tetradecanoylphorbol-13-acetate; T2, 3,3′-diiodothyronine; rT3 (reverse T3), 3,3′,5′-triiodothyronine; T3, 3,5,3′-triiodothyronine; 5-HIAA, 5-hydroxyindoleacetic acid; $LOO^{\bullet}$, A lipid peroxyl radical; AChE, acetylcholinesterase; ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; ACTH, adrenocorticotrophin; AO-FTF, after onset of fetal thyroid function; AIT, amiodarone-induced thyrotoxicosis; $AscH^{-}$, ascorbate monoanion; $Asc^{\bullet -}$, ascorbyl radical; BO-FTF, before onset of fetal thyroid function; BDNF, brain-derived neurotrophic factor; BAT, brown adipose tissue; CMZ, carbimazole; CAT, catalase; CA, catecholamine; CNS, central nervous system; CSF, cerebrospinal fluid; ChAT, choline acetyltransferase; CD, conjugated dienes; CRF, corticotropin-releasing factor; cAMP, cyclic adenosine monophosphate; d-AAO, d-amino acid oxidase; GD, days of gestation; DHLA, dihydrolipoic acid; DIT, diiodotyrosine; DDC, DOPA decarboxylase; DA, dopamine; EGL, external granule cell layer; ECM, extracellular matrix; FGF, fibroblast growth factors; fT4, free thyroxine; GABA-T, GABA-transaminase; γ-GCS, gamma-glutamyl synthetase; G6PD, glucose 6-phosphate dehydrogenase; GCL, glutamate cysteine ligase; GCLC, glutamate cysteine ligase catalytic subunit; GCLM, glutamate cysteine ligase smaller modulator subunit; GAD, glutamic acid decarboxylase; GSH, glutathione; GSSG/2GSH, glutathione disulphide-glutathione couple; GPx, glutathione peroxidase; GSSGR, glutathione reductase; GST, glutathione-*S*-transferase; GD, Graves' disease; hCG, human chorionic gonadotrophin; H_2O_2, hydrogen peroxide; HOCl, hypochlorous acid; HPt, hypothalamohypophysial-thyroid axis; IRD, inner ring deiodination; IGL, internal granule cell layer; ID, iodine deficiency; IDD, iodine deficiency disorders; $L^{\bullet}$, lipid radical; $LO^{\bullet}$, lipid alkoxyl radical; LH, polyunsaturated fatty acid; ALA, lipoic acid; MMI, methimazole [1-methyl-2-mercaptoimidazole tapazole]; MAPs, microtubules associated proteins; MIT, monoiodotyrosine; MAO, monoamine oxidase; MAO-A, monoamine oxidase type A; NGF, nerve growth factor; NGFR, nerve growth factor receptor; N-CAM, neural cell adhesion molecule; $NO^{\bullet}$, nitric radical; NA, noradreneraline; O-2A, oligodendrocyte type II astrocyte; ODC, ornithine decarboxylase activity; ORD, outer ring deiodination; GSSG, oxidized glutathione; PRTH, pituitary resistance to thyroid hormone; PND, postnatal day; PPT, postpartum thyroiditis; PTU, propylthiouracil; T-$O^{\bullet}$, radical of Vitamin E; Rob, Raphe obscurus; Rpa, Raphe pallidus; ROS, reactive oxygen species; RLS, restless legs syndrome; 5-HT, serotonin; 5-HT_{1A}, serotonin receptor type 1A; 5-HT2, serotonin receptor type 2; SRIH, somatostatin; SSDH, succinate semialdehyde dehydrogenase; SOD, superoxide dismutase; TBARS, thiobarbituric acid-reacting substances; SH, thiol groups; TBG, thyroglobulin; TR, thyroid hormone nuclear receptor; TRα, thyroid hormone receptor α; TRsthyroid hormone receptors; THs, thyroid hormones; THOX, thyroid oxidase; TPO, thyroid peroxidase; TX, thyroidectomized; TSH, thyrotropin; TRH, thyrotropin-releasing hormone or thyroid releasing hormone; T4, thyroxine 3,5,3′,5′-tetraiodothyronine; t-SH, total thiol; TTR, transthyretin; T3, 3,5,3′-triiodothyronine; TSHomas, TSH-producing pituitary tumors; D1, Type I deiodinase; D2, Type II deiodinase; D3, Type III deiodinase; TyrH, tyrosine hydroxylase; GABAγ, -aminobutyric acid; γ-GTγ, -glutamyl transpeptidase; ALA, Alpha Lipoic acid; Dopa, L-dihydroxylphenyl-alanine; GSH, Glutathione reduced form; GSSG, Glutathione oxidizes form; GAT-1, GABA transporter1.

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shifts in the relative development of several central transmitter systems that leads to a multitude of irreversible morphological and biochemical abnormalities (pathophysiology). Thus, further studies need to be done to emphasize this concept.

Keywords: Thyroid hormones and brain development

Contents

1. Introduction

In the last 15 years, an increasing number of studies have indicated that thyroid hormones [thyroxine (T4); 3,5,3′-triiodothyronine (T3)] have important physiological functions, not only during brain maturation but also in the adult vertebrate brain (Broedel et al., 2003). Several reports have been published on the essential role of the thyroid hormones for mammalian and non-mammalian brain development (Ninfalr et al., 1887; Eayrs, 1971; Myant, 1971; Grave, 1977; Krude et al., 1977; Klein, 1980; Dussault and Walker, 1983; Schwartz, 1983; Legrand, 1986; Dussault and Ruel, 1987; Timiras and Nzekwe, 1989; Porterfield and Hendrich, 1991; Stein et al., 1991; Boyages and Halpern, 1993; Miculan et al., 1993; Porterfield and Hendrich, 1993; DeLong et al., 1994; Porterfield and Stein, 1994; Bernal and Nunez, 1995; Brown et al., 1995; Foley, 1996; Calzà et al., 1997; Escobar et al., 1997; Morreale de Escobar et al., 1997; Oppenheimer and Schwartz, 1997; Pickard et al., 1997; Puymirat, 1997; Sinha et al., 1997; Strait et al., 1997; Takeuchi et al., 1998; Thompson, 1999; Alvarez-Dolado et al., 2000; Chan and Kilby, 2000; Delange, 2000; Koibuchi and Chin, 2000; Thompson and Potter, 2000; Anderson, 2001; Berbel et al., 2001; Calloni et al., 2001; Hashimoto et al., 2001; Morreale de Escobar, 2001; Moscicka and Gadzinowski, 2001; Yen, 2001; Bernal, 2002; Forrest, 2002; Leitolf et al., 2002; Lorenzo et al., 2002; Ogilvy-Stuart, 2002; Zoeller et al., 2002; Bernal et al., 2003; Darbra et al., 2003; Gilbert and Paczkowski, 2003; Alva-Sánchez et al., 2004; Bahls and de Carvalho, 2004; Kester et al., 2004; Martinez-Galan et al., 2004; Quignodon et al., 2004; Sethi and Kapil, 2004; Yilmazer-Hanke et al., 2004; Zoeller, 2004; Bansal et al., 2005; Bruno et al., 2005; Dong et al., 2005;

Incerpi, 2005; Kimura-Kuroda et al., 2005; Negishi et al., 2005; Pacheco-Rosado et al., 2005; Rudas et al., 2005; Zoeller, 2005; Gilbert and Sui, 2006; Hamanna et al., 2006; Koibuchi, 2006; Mori et al., 2006; Nelson and Habibi, 2006; Zhang et al., 2006; Farahvar et al., 2007; Hogan et al., 2007; Jansen et al., 2007; Setia et al., 2007; Zamoner et al., 2007). Normal brain development requires the presence of thyroid hormones that are essential for cell migration, dendrite and axon outgrowth, synapse formation, myelination and gliogenesis (Lima et al., 1997; Oppenheimer and Schwartz, 1997). It is now well established that the mammalian brain is a direct target organ of thyroid hormone, both during development and in adult individuals.

The best-defined animal model of thyroid hormone-dependent brain development is the neonatal rat (Schwartz et al., 1997; Legrand, 1986). Probably, the main reason is the interspecies differences in developmental schedules. The rat is an altricial species, born with a relatively undeveloped brain and with the thyroid–pituitary–hypothalamic axis not yet fully matured (Oppenheimer and Schwartz, 1997). The sheep, in contrast, is a precocial animal born with a relatively advanced state of brain maturation. Development of the ovine thyroid–pituitary axis is nearly complete at birth (Fisher, 1991). In this sense, brain development in rodents occurs early, relative to humans. For example, the rat brain at birth is at the same stage as the human brain at 5–6 months of gestation, and the rat brain at 10 days of postnatal age is equivalent to the human brain at birth (Porterfield and Hendrich, 1993). In fact, Fisher and Polk (1988) and Stein et al. (1991) have extensively discussed the contrasting patterns of development in these species. Whereas there is evidence of a role for thyroid hormone in brain maturation during the intrauterine period in human (Pharoah et al., 1971; Grant et al., 1992; Boyages and Halpern, 1993) and sheep (McIntosh et al., 1979, 1982), this is not yet clearly established in the rat.

Thyroid gland produces T4 and T3 and these hormones have two predominant functions (DeVito et al., 1999). The first is a critical role in growth and development. One of the clearest examples of the importance of THs in growth and development is the metamorphosis of amphibians, in particular the metamorphosis of tadpoles into frogs (Kollros, 1961; Kaltenbach, 1966; Dodd and Dodd, 1976). Other examples of the importance of THs in development are the transformation of salmon from freshwater-dwelling par to seawater-dwelling smolts (Dickhoff and Sullivan, 1987; Specker, 1988), flounder metamorphosis (Inui and Miwa, 1985), and development of the central nervous system in humans and other mammals (Dussault and Ruel, 1987; Bernal and Nunez, 1995). The second major function of THs is to maintain metabolic homeostasis in mammals (Farrell and Braverman, 1995). Furthermore, thyroid hormones, acting through thyroid hormone receptors (TRs) and play an important role in amphibian metamorphosis and vertebrate development (Nagasawa et al., 1997). These receptors are expressed in neurons, oligodendrocytes, and astrocytes, the predominant cell types in the brain (Mellström et al., 1991; Strait et al., 1991, 1997; Bradley et al., 1992; Carlson et al., 1994; Carre et al., 1998). Taking into account that thyroid hormone exerts specific effects on brain development by regulating gene expression (Oppenheimer and Schwartz, 1997; Zhang and Lazar, 2000), some studies demonstrate that several genes are regulated directly by thyroid hormones at the transcriptional level and at an earlier stage of cerebellar development, i.e., during embryonic day 18–postnatal day 0 (Alvarez-Dolado et al., 1999). It is clear that the fetus and neonate are quite sensitive to thyroid hormone.

Furthermore, hypo- or hyperthyroidism affects the maturation of the CNS and causes irreversible dysfunction of the brain if not corrected shortly after the birth of both rodents and humans (Wong and Leung, 2001). This late effect of neonatal hypo-hyperthyroidism on the CNS is probably leading to defective neuronal circuit formation. In addition, both hyper- and hypothyroidism are known to affect directly or indirectly the proliferation, apoptosis, migration, and differentiation of several neuronal and glial cell types during the postnatal brain development (Lauder, 1977a,b; Bernal and Nunez, 1995; Oppenheimer and Schwartz, 1997). At a biochemical level, thyroid hormone dysfunction may affect not only gene expression but also the characteristics of various neurotransmitter systems (Mason et al., 1987, 1990). Therefore, this review will deal with three important topics, sometimes controversial and which still are not completely settled: what are the cellular targets of thyroid in brain, what is the different states of the thyroid hormones on the brain development, and during which periods of development are thyroid hormones important. Also, the goal of this review is to place the exciting advances that have occurred by the previous authors.

2. Thyroid hormones and fetal brain development

When the development of the nervous system is viewed with respect to the influence of thyroid hormones, three developmental periods can be defined as a following in Table 1 (Porterfield and Hendrich, 1993; Çalikoğlu, 1999).

2.1. Thyroid histology and endocrinology

The thyroid gland is primarily composed of a single cell type, the thyroid follicular cell (Gorbman and Bern, 1962). These cells form colloid-filled follicles, produce thyroid hormone, store it in the colloid-filled lumen of the follicle and control the release of the hormone from the colloid into the blood stream. Thyroid hormone production starts with the synthesis of thyroglobulin (TBG). The iodothyronines are formed in the thyroid gland from two iodinated tyrosyl residues on the large hormone ‘‘precursor’’, TBG (Taurog, 1996). Then TBG is secreted into the colloidal lumen of the follicle where tyrosine residues are iodinated and where it is condensed to produce T3 and T4 (Frieden and Lipner, 1971). T3 and T4 remain covalently bound to thyroglobulin as long as they are stored in the colloid (Wendl et al., 2002), and the bound forms of T3 and T4 are eventually taken up by the follicular cells and proteolytically separated from the thyroglobulin. Then free T3 and T4 are released and act as thyroid hormones. The most important iodothyronines are 3,5,3′,5′-tetraiodothyronine

Table 1
The influence of thyroid hormones on the development of the nervous system

Phase I	Phase II	Phase III
Represents the first 10–12 weeks of gestation in human, and the first 17 days of gestation in rat and represents the time before the synthesis of fetal thyroid hormones	Spans the second and third trimester of human gestation and the last four days of rat gestation	Is the period after birth
Any exposure of the brain to thyroid hormones during this period must come from the mother and it is not known if THs play a direct role in neurological development in this period	During this period, the fetal thyroid is actively synthesizing and releasing thyroid hormones, and thus the developing fetal brain is exposed to fetal thyroid hormones and perhaps maternal hormones	During this period the brain is dependent upon thyroid hormones secreted by the neonates thyroid
Most of the brain stem and a significant portion of cerebral neurogenesis occur during this phase		This phase in rats encompasses a period when much of neuronal proliferation, migration and differentiation occur in the cerebellum While forebrain neurogenesis and migration are essentially complete by this time, this is an important period for forebrain neuronal differentiation and myelination -Each of these events is known to be dependent upon normal thyroid hormone levels during this period
Neuronal migration also occurs during this phase, but significant neuronal maturation, neurite formation and synaptic development in the forebrain has not yet begun		

(thyroxine, T4), 3,5,3′-triiodothyronine (T3), and 3,3′,5′-triiodothyronine (reverse T3; rT3) as in Fig. 1.

During development, the thyroid follicular cells derive from the endoderm (Noden, 1991; Walker and Liem, 1994). Thyroid development is classically subdivided into a few distinguishable steps, primarily based on observations in mammals (Wendl et al., 2002): first, a group of cells buds off the floor of the primitive pharynx. Second, these cells reposition dorsocaudally to reach the anterior wall of the trachea. Third, the precursor cells proliferate and, fourth, differentiate into thyroid follicular cells (Macchia, 2000). In addition, other cells, including neural crest derived C cells, merge with the group of endoderm-derived precursor cells (Manley and Capecchi, 1998). In humans, any disorder of the thyroid that leads to reduced thyroxine production at birth is called congenital hypothyroidism (Macchia, 2000). Although disturbed embryonic development of the thyroid gland leads to congenital hypothyroidism in humans and mammals, the principles of thyroid organogenesis are largely unknown (Wendl et al., 2002). In fact, the length of

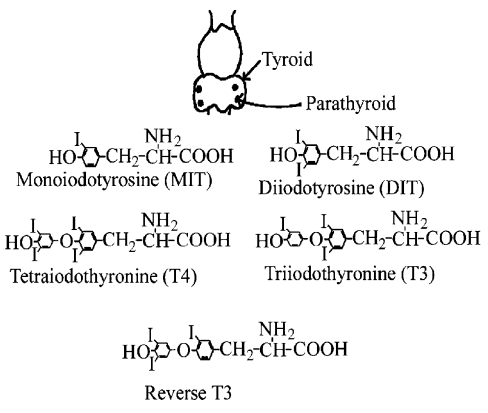

Fig. 1. Bilobed structure of thyroid around the trachea below the pharynx and the structural formula of its hormones and precursor compounds.

the gestation period and the degree of neonatal maturity influences the development of the thyroid gland. The animals having short gestation period show a postnatal activity of the thyroid gland (Hall and Kaun, 1942; Mitskavitch, 1957). In contrast, the animals having long gestation period as camel (12–13 months) the secretory activity of the thyroid gland begins during the later stages of prenatal development (El-Gharbawy, 1986). Therefore, several authors (Fahmy and Moustafa, 1965; Ewais et al., 1982; El-Gharbawy, 1986; Okada et al., 1990) studied the thyroid gland of large animals. Moreover, some investigations were carried out on the prenatal and postnatal development of the thyroid glands of laboratory animals as in guinea pig (Ries and Allegretti, 1965; Juhl, 1981a,b; Kameda, 1986), in opossum (Krause and Cutts, 1983), in golden hamster (Wollman and Nerve, 1971; Taniguchi et al., 1990) and in rats (Calvert and Isler, 1970; Mansour et al., 1985). In rabbit, Waterman and Gorbman (1956) studied the prenatal development of the thyroid gland while El-Shammaa (1996) studied the pre- and postnatal development of the thyroid gland. In addition, the effect of age-related changes in thyroid structure and function was studied in Sprague–Dawley rat (Rao-Rupanagudi et al., 1992), in red-winged blackbird (Olson et al., 1999), in guinea pig, cat, dog, pig, horse and adult cow (Tomonari, 1959), in rainbow trout embryos (Raine and Leatherland, 2000), and in human (Chan and Conen, 1971; McMillian et al., 1974; Fraser and Dckworth, 1979; Norris, 1980; Harach, 1987; Bocian-Sobkowska et al., 1992; Donald-Gordon, 2003). Thus, the aging process is associated with a number of thyroid function changes. The question of whether and to what extent these changes are expression of the aging process per se or of an age-associated thyroidal and nonthyroidal illness is a matter of debate. Also, Hulbert (2000) reported that; (1) thyroid hormones are strongly associated with membranes in tissues and normally rigidify these membranes; (2) they also affect the acyl composition of

membrane bilayers and it is suggested that this is due to the cells responding to thyroid-hormone-induced membrane rigidificataion; and (3) at physiological pH, the dissociation of the phenolic –OH group of these iodothyronines is an important determinant of their physical chemistry that impacts on their biological effects.

On the other hand, circulating triiodothyronines are formed largely from peripheral deiodination of T4, which is the major product released from the thyroid gland (Leonard and Koehrle, 1996). The pituitary glycoprotein hormone, thyrotropin (TSH) (Wondisford et al., 1996), regulates the synthesis and secretion of thyroid hormones by activating guanylate cyclase in thyroid follicular cells (Rapoport and Spaulding, 1986). However, there are a number of important extrathyroidal processes that maintain circulating thyroid hormones within a relatively narrow concentration range (Leonard and Koehrle, 1996). Normal variation in circulating concentrations of T4 reflects short-term pulsatile and diurnal variation (Stockigt, 1996). T4 and/or T3 exert a negative feedback effect on pituitary secretion of TSH (Scanlon and Toft, 1996), and on the hypothalamic secretion of the releasing factor, thyrotropin-releasing hormone (TRH) (Koller et al., 1987; Rondeel et al., 1988), which controls the amount of TSH in the blood. Indeed, TRH from the hypothalamus stimulates the pituitary gland to release TSH (Jackson and Lechan, 1983), and modulates the sensitivity of the pituitary gland to negative feedback by thyroid hormone (Greer et al., 1993). Also, as shown in (Fig. 2), T3 acts via binding to the thyrotroph nuclear T3 receptor, and T4 mainly acts via its intra-pituitary or intra-hypothalamic conversion to T3, although a direct negative effect of T4 independent from local T3 generation has been recently reported on TSH-β gene expression (Bogazzi et al., 1997). Both regulate the synthesis and release of TSH at the pituitary level, as well as indirectly affecting TSH synthesis via their effects on the synthesis of TRH and other neuropeptides. The TRH mainly acts by activating the phospatidylinositol-protein kinase C pathway (Bogazzi et al., 1997). Therefore, the major regulators of TSH production are represented by the inhibitory effects of thyroid hormone (Reichlin and Utiger, 1967) and by the stimulatory action of TRH. Other hormones/factors are also implicated in the complex regulation of TSH-β gene expression, as detailed below in (Fig. 2) (Bogazzi et al., 1997). Moreover, Fuse et al. (1990) suggested that: (1) The thyroid hormone feedback control of pituitary TSH release in the extremely premature infants begins to mature after 6 weeks of postnatal age. (2) The maturation pattern of the hypothalamic–pituitary–thyroid system in premature infants is similar to that of the intrauterine fetus. Hashimoto et al. (1991) indicated that the maturation of the pituitary–thyroid axis is intrinsically controlled by gestational age rather than by serum thyroid hormone levels. The hypersecretion of TSH in preterm infants induces a progressive increase in serum thyroid hormones, and although there is individual variation in the maturation process, the feedback regulation of the pituitary–thyroid axis matures by approximately the 37th gestational week (Hashimoto et al., 1991). Thus, a number of processes control circulating levels of thyroid hormones and the balance between different forms of these hormones.

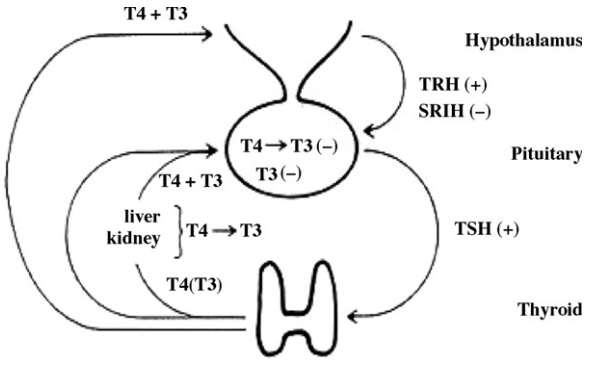

Fig. 2. Basic elements in the regulation of thyroid function. TRH is a necessary tonic stimulus to TSH synthesis and release. TRH synthesis is regulated directly by thyroid hormones. T4 is the predominant secretory product of the thyroid gland, with peripheral deiodination of T4 to T3 in the liver and kidney supplying roughly 80% of the circulating T3. Both circulating T3 and T4 directly inhibit TSH synthesis and release independently; T4 via its rapid conversion to T3. SRIH, somatostatin (Bogazzi et al., 1997).

In nearly, all vertebrates synthesis and release of T4 is under the control of the hypothalamohypophysial-thyroid axis (HPT) (Degitz et al., 2005), and TRH is released from cells in the hypothalamus and is transported via portal circulation to the pituitary, where it stimulates a subpopulation of secretory cells, thyrotropes, to synthesize and release TSH. Thyroid-stimulating hormone travels via systemic circulation to the thyroid gland and stimulates thyroid cells to synthesize and release thyroid hormones into systemic circulation. The HPT in adult anurans follows this general vertebrate pattern (Dodd and Dodd, 1976). However, there are differences in the larval life stage with regard to stimulation of the thyrotropes by the hypothalamus. The corticotropin-releasing factor (CRF), rather than TRH, may be the primary hypothalamic signal which initiates TSH synthesis and release (Denver, 1996). T4 and T3 associate with serum proteins and are carried throughout the body to target tissues, where they cross the cell membranes and are subject to 5′- and 5-deiodinase activity (Degitz et al., 2005). In tissues programmed to do so, the relatively inactive T4 is converted by 5′ deiodination to the active form of the hormone, T3, which binds to nuclear receptors and initiates gene transcription (Norris, 1997). 5-Deiodinase, deiodinates the tyrosyl ring of T4 and T3 to affect the production of rT3 and diiodothyronines, respectively, inactive forms of T4. This can result in reductions in local T3 concentration and is thought to prevent inappropriate T4 stimulation throughout the metamorphic process (Becker et al., 1997; Huang et al., 1999; Kawahara et al., 1999; Marsh-Armstrong et al., 1999). In mammals, the hormones are subject to conjugation and ultimately elimination, via sulfation and glucuronidation, and catabolism of the tyrosine residue via decarboxylation and deamination (Brucker-Davis, 1998). However, the roles of these processes in anuran metamorphosis are poorly understood. Theoretically, normal T4 homeostasis and action can be disrupted at several sites in the pathway, including: interference of the negative feedback loop, T4 synthesis, T4 transport, metabolic conversion of T4 to active and inactive forms,

receptor-mediated effects, and nonspecific effects (Degitz et al., 2005). Thus, alterations in thyroid hormone homeostasis may result from disturbances in thyroid hormone synthesis, secretion, or catabolism (Capen, 1997, 1998). For example, disturbances may occur as a result of inhibition of iodine uptake or via increased thyroid hormone clearance. An alteration in thyroid hormone homeostasis can also occur as a result of induced hepatic microsomal enzymes or by an inhibition of 5′-deiodinase, the intracellular enzyme responsible for converting T4 to T3 (Masaki et al., 1984; McClain et al., 1989; Capen, 1997). Generally, the synthesis and secretion of the thyroid hormones depend on the presence of iodine and tyrosine as well as the maturation of the hypothalamic–pituitary–thyroid axis system (Kirsten, 2000). The medulla also contains the most abundant groups of TRH synthesizing neurons outside of the hypothalamus, which are located in the raphe nuclei, including the raphe pallidus (Rpa) and the raphe obscurus (Rob), and the parapyramidal regions (PPR) (Kachidian, 1991).

An important feature of TH is the broad multiplicity of its physiological actions in vertebrates, from fish to reptiles to amphibia to birds and mammals (Pitt-Rivers and Tata, 1959; Gorbman and Bern, 1962). As summarized in Table 2, these can be broadly divided into two classes of actions, according to whether the hormone regulates processes in adult life or when the organism is undergoing development (Tata, 2006); (1) In adult mammals, TH controls basal metabolic rate and energy metabolism, while in most vertebrates it regulates metabolic processes involving nitrogen balance, lipid degradation, etc. (2) In developing vertebrates, particularly during post-embryonic development, neurogenesis and all processes concerned with maturation of the central nervous system are highly dependent on the availability of maternal or fetal TH, as exemplified by cretinism, which is a well-known disorder of hormonal deficiency during human fetal development. Therefore, there are morphological and functional maturation of many tissues, such as bone, liver, blood and skin in both warm- and cold-blooded vertebrates. However, no developmental action of thyroid hormone is as dramatic as the initiation and progression of amphibian metamorphosis (Gilbert et al., 1996; Tata, 1998; Shi, 1999).

Generally, the synthesis and storage of TH predominately occurs in the thyroid gland and the most of the TH in the thyroid is present as T4 (DeVito et al., 1999). Although a small proportion of thyroid-localized TH is T3, most T3 comes from the deiodination of T4 by tissue specific deiodinases. The processes involved in the synthesis, storage, release, transport, and metabolism of THs are complex and consist of several steps as a following (DeVito et al., 1999): (1) uptake of iodide ion by the thyroid gland; (2) oxidation of iodide and the iodination of tyrosine residues within thyroglobulin; (3) coupling of iodotyrosine residues to produce iodothyronines; (4) proteolysis of thyroglobulin and release of T4 and T3 into the blood; (5) binding to serum transport proteins; (6) target tissue synthesis of T3 from T4; (7) catabolism of T4 and T3 in peripheral tissues; and (8) catabolism and biliary elimination of THs in the liver. Actually, there are many examples of pharmaceutical, environmental, and naturally occurring chemicals that alter one or more of these processes in mammals or interfere with the production, transport, and metabolism of these hormones; they have been reviewed by Gaitan (1986), Hill et al. (1989), Atterwill and Aylward (1995), Brucker-Davis (1998).

Interestingly, in adult, thyroid hormones enter the brain through two routes (Porterfield, 2000); (1) The predominant route is via the blood–brain barrier involving direct transport through the capillary endothelium and into the brain cells. Hormone transport via this route depends on the serum hormone levels (influenced by serum protein-binding relationships), the transport systems through the endothelium, and the transport systems into the brain cells. (2) The second and less significant route is via the choroid plexus–cerebrospinal fluid (CSF). The thyroid hormone-binding protein transthyretin (TTR) binds T4 but not T3. It produced by the choroid plexus and secreted into the CSF. The TTR then binds to T4 that enters CSF through the choroid plexus and may play an important role in T4 transport to the brain cells.

2.2. Deiodination types

The deiodination process catalyzed by three deiodinases; I, II and III deiodinase (D1, D2, and D3). In birds, as in mammals, so far three types of deiodinases have been identified. The type I deiodinase (D1), which is capable of both outer ring deiodination (ORD) and inner ring deiodination (IRD) (Van der Geyten et al., 1997). The type II deiodinase (D2), which is only capable of ORD (Gereben et al., 1999). Also the type III deiodinase (D3), which exclusively catalyses IRD (Valverde et al., 1993). Three types of membrane-bound cellular deiodinase enzyme systems in vertebrates produce various iodothyronines, the distribution of deiodinases varies between tissues, and each has a distinct developmental profile (Hulbert, 2000). However, two of them are present in amphibians: type II (D2) with ORD activity and type III (D3) with IRD activity (Darras et al., 2002). Therefore, the characteristics of these types will show on the following Table 3.

Table 2
Multiplicity of physiological and biochemical actions of thyroid hormone

Growth and developmental actions	Metabolic actions
Rate of postnatal growth of many mammalian and avian tissues	Regulation of basal metabolic rate in homeotherms
Functional and biochemical maturation of fetal brain and bone	Movement of water and Na^+ ions across cell membranes calcium and phosphorous metabolism
Morphogenesis, gene switching and cell death in amphibian metamorphosis	Regulation of metabolism of cholesterol and other lipids
Control of moulting in birds	Nitrogen (urea, creatine) metabolism
Regulation of synthesis of mitochondrial respiratory enzymes and membranes	Control of oxidative phosphorylation and energy metabolism

Table 3
The characteristic types of deiodination

Compare-face	D1	D2	D3
(1) Main forms	T4–T3, rT3–T2	T4–rT3, T3–T2	T4–rT3–T2
(2) Expression	In liver, kidney, thyroid (Kohrle, 1999; Bianco et al., 2002). D1 is not expressed in cells of the central nervous system	In brain, pituitary, brown adipose tissue, human thyroid, and skeletal muscle (Croteau et al., 1996; Salvatore et al., 1996; Bartha et al., 2000; Bianco et al., 2002)	In brain, skin, fetal tissues, placenta, and uterus and at other sites of the maternal-fetal interface, such as the umbilical arteries and vein (Kaplan and Shaw, 1984; Koopdonk-Kool et al., 1996; Galton et al., 1999; Huang et al., 2003). D3 is predominantly present in neuronal cells (Escamez et al., 1999; Tu et al., 1999), which are the main cells that express thyroid hormone receptors (Leonard et al., 1994; Carlson et al., 1996)
(3) Function	Production serum T3 and the clearance of serum rT3 (Bianco et al., 2002)	It catalyzes the outer ring deiodination of T4 to T3 and is thus important for the local production of T3 (Zoeller, 2004)	Catalyzes the inner ring deiodination of T4 to rT3 and of T3 to 3,3′-T2 (Kohrle, 1999)
(4) Activites and regulations on			
Hypothyroidism	Decrease (Zoeller, 2004)	Increase (Croteau et al., 1996)	Decrease (Zoeller, 2004)
Hyperthyroidism	Increase (Zoeller, 2004)	Decrease (Croteau et al., 1996)	Increase (Zoeller, 2004)

Moreover, in the hypo- or hyperthyroid state, whole brain T3 content is altered to a considerably lesser extent than observed in other organs, such as the liver (Dratman et al., 1983; van Doorn et al., 1984). This relative stability of brain T3 level appears to be due at least in part to autoregulatory mechanisms within the brain itself that regulate both T4 to T3 conversion (Crantz and Larsen, 1980; van Doorn et al., 1983) and the metabolism of T4 and T3 to inactive compounds (Kaplan, 1984). For example, the fractional conversion of T4 to T3 in brain is increased in the hypothyroid state, whereas it is decreased by this condition in the liver (van Doorn et al., 1983, 1984). The type 2 iodothyronine 5′-deiodinase appears to be an important factor in the ability of the central nervous system to adapt to alterations in thyroid hormone status (Burmeister et al., 1997). This enzyme, which is present in the anterior pituitary gland and brown adipose tissue as well as in several regions of the brain (Kaplan, 1980; Kaplan and Yaskoski, 1981; Kaplan et al., 1981), deiodinates T4 at the 5′-position to form T3 and appears to be the principal source of intracellular T3 in these tissues (van Doorn et al., 1983). D2 activity is rapidly and markedly altered by changes in thyroid hormone levels; hypothyroidism results in enhanced activity, whereas the opposite effect occurs in hyperthyroidism (Kaplan et al., 1981). Furthermore, it has recently been reported that 90% of T3 production in hypothyroid rats occurs in slowly exchanging tissues, such as brain and brown adipose tissue (BAT), where D2 predominates as the enzyme catalyzing T4 to T3 conversion (Di Stefano et al., 1996). Several lines of evidence strongly suggest that posttranslational mechanisms are involved in the regulation of D2 activity by thyroid hormone (St Germain, 1988; Farwell et al., 1990). Specifically, thyroid hormones have been observed both *in vivo* in rodents and in several cell culture systems to induce a decrease in D2 activity that is more rapid than that observed when gene transcription or protein synthesis is blocked with actinomycin D or cycloheximide, respectively (Silva and Larsen, 1986; St Germain, 1988). In addition, T4 and rT3 are considerably more potent that T3 in inducing inactivation of D2 when administered acutely to hypothyroid animals (Silva and Larsen, 1986; Obregón et al., 1986). Given that transcriptional regulation by thyroid hormone is primarily, if not exclusively, mediated by T3 binding to its nuclear receptors (Oppenheimer et al., 1995). The greater potency of T4 and rT3 in acutely inhibiting D2 activity is further evidence that this process involves extranuclear metabolic events such as alterations in the rate of D2 protein turnover or translocation of the enzyme between various cellular compartments (St Germain, 1988; Farwell et al., 1993).

In addition, the basic deiodinase reactions are shown in Fig. 3 (Bianco and Kim, 2006). The reactions catalyzed by the deiodinases remove iodine moieties (spheres) from the phenolic (outer rings) or tyrosil (inner rings) rings of the iodothyronines. These pathways can activate T4 by transforming it into T3 (via D1 or D2) or prevent it from being activated by converting it to the metabolically inactive form, reverse T3 (via D1 or D3). T2 is an inactive product common to both pathways that is rapidly metabolized by further deiodination. In addition, Serum thyroid hormone concentrations are generally low during development, and the contrast between serum and tissue T3 content afforded by the deiodinases is thus particularly critical for developing structures (Galton, 2005; St Germain et al., 2005). Signaling via thyroid hormone is tightly regulated both spatially and temporally via the expression pattern of deiodinases and the thyroid hormone-inactivating D3 pathway is highly stimulated during development, with a tissue distribution much broader than that in adults (Bianco and Kim, 2006). Thus, the expression pattern of D3 limits thyroid hormone signaling locally in developing structures and systemically by lowering serum T3 concentrations.

2.3. Role of maternal thyroid hormones

2.3.1. In normal case

Commonly, thyroid hormones are essential for normal neonatal development in both humans and rodents (Çalikoğlu, 1999) and the experimental work indicated that thyroid

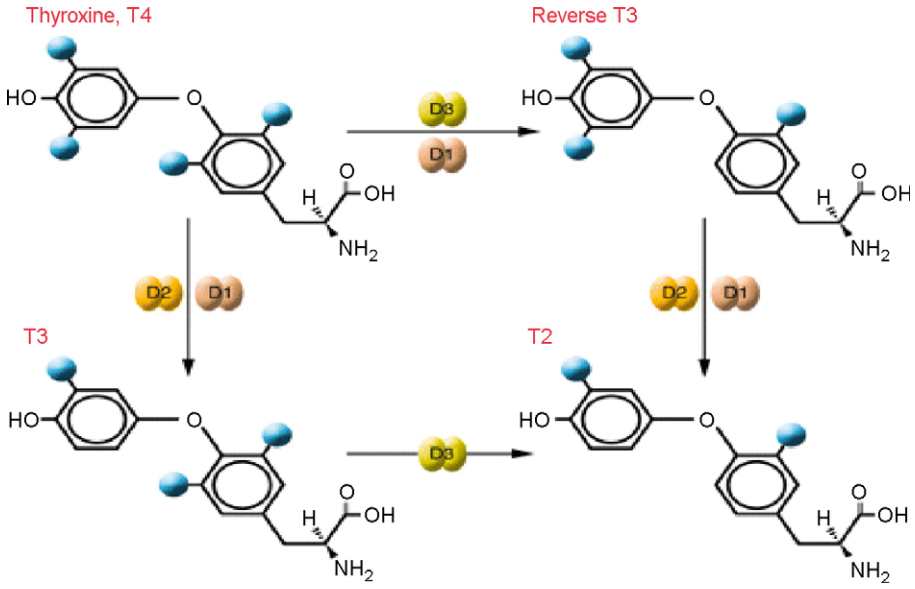

Fig. 3. The basic deiodinase reactions (Bianco and Kim, 2006).

hormones are transported from the mother to the fetus, albeit in limited amounts, and that the fetal brain is exposed to thyroid hormones before initiation of fetal thyroid hormone synthesis. In addition, the maternal thyroid hormone regulates early fetal brain development in human and animal models (Porterfield and Hendrich, 1991; Morreale de Escobar et al., 1997; Pickard et al., 1997; Sinha et al., 1997). However, until recently, it was generally believed that the effects of thyroid hormone on brain development occur only after birth (Fisher, 1999). Several recent clinical observations provide evidence to the contrary. First, thyroid hormone of maternal origin crosses the placenta and reaches the fetus (Vulsma et al., 1989; Contempré et al., 1993). In addition, the thyroid receptors (TRs) are expressed in the fetal brain before the onset of fetal thyroid function, and receptor occupancy is within the range known to elicit physiological effects (Bernal and Pekonen, 1984; Ferreiro et al., 1988). Second, iodine therapy prevents neurological cretinism in regions of endemic goiter only if initiated before the beginning of the third trimester (Cao et al., 1994). In rat, the thyroid hormone of maternal origin can reach the fetus (Morreale de Escobar et al., 1988) and that TRs are expressed in the fetal rat brain before the onset of fetal thyroid function (Morreale de Escobar et al., 1988; Falcone et al., 1994). Thus, the thyroid hormones are essential for brain maturation from early embryonic stages onward (Bernal and Nunez, 1995; Morreale de Escobar et al., 2000). However, TH-dependent stages of fetal brain development remain to be characterized. Notably, the maternal thyroid is the only source of T4 and T3 for the brain of the fetus because its thyroid gland does not start contributing to fetal requirements until midgestation in man, and days 17.5–18 in rats (Ausó et al., 2004). Therefore, the amount of maternal T4 that the fetus receives early in pregnancy will determine thyroid hormone action in its brain because it depends on maternal T4 for its intracellular supply of the active form of the hormone, T3. However, fetal brain total T3 levels are low (ca. 100 pM) at this time (Ferreiro et al., 1988), but receptor occupancy approximates 25% since free T3 concentrations are high in the nucleus relative to the cytosol (Ferreiro et al., 1988). In rats, maternal T4, but not T3, replacement will elevate fetal brain thyroid hormone levels (Calvo et al., 1990) (see Fig. 5). Maternal thyroid hormone may therefore directly influence the early fetal brain development, however because it also accumulates within maternal tissues and the placenta (Morreale de Escobar et al., 1985), indirect mechanisms of regulation may be important. Placental maldevelopment has been reported in some (Bonet and Herrera, 1988; Porterfield and Hendrich, 1991) but not all publications (Morreale de Escobar et al., 1985). Regarding to Fig. 4, materno-fetal transfer of thyroid hormones has been demonstrated in early fetal stages (Contempré et al., 1993; Chan and Kilby, 2000) and continues, at least in the case of fetal inability, to produce sufficient thyroid hormone until term (Vulsma et al., 1984). Actually, brain cells can protect themselves against higher fetal T4 and T3 values by decreasing

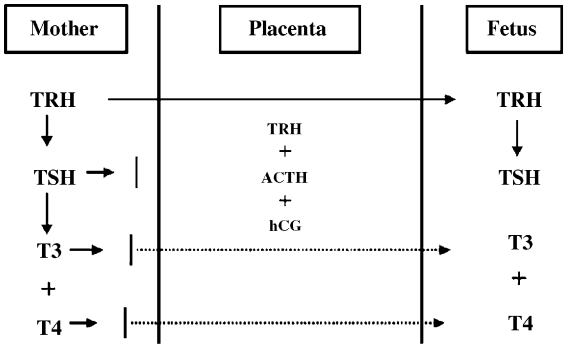

Fig. 4. Classically the placenta has been considered as a 'barrier' to transfer of free T3 and T4 to the fetus. However, recent epidemiological data has rekindled interest as to the possibility of transplacental transfer of thyroid hormones to the fetus from early gestation (TRH, thyroid releasing hormone; TSH, thyrotrophin; T3, triiodothyronine; T4, thyroxine; ACTH, adrenocorticotrophin; hCG, human chorionic gonadotrophin) (Chan and Kilby, 2000).

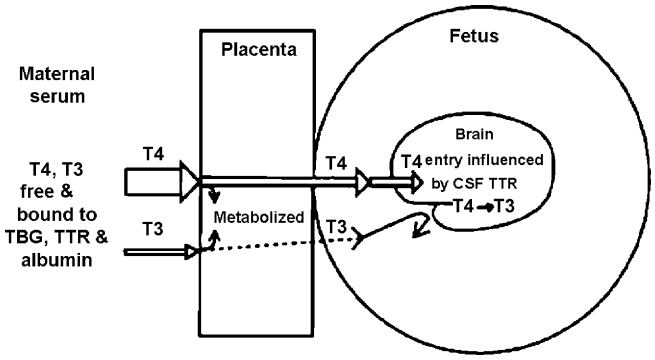

Fig. 5. Potential sources of fetal brain thyroid hormones prior to the beginning of fetal thyroid function. The availability of maternal thyroid hormones (T4, T3) to the placenta depends upon both serum levels and the extent of serum binding of the hormones. Once crossing the placenta, thyroid hormones must reach the brain. The predominant source of fetal brain thyroid hormones has been shown to be fetal serum T4, not T3. Cerebrospinal fluid TTR binding of thyroid hormones may be important in providing thyroid hormones to the fetal brain. Once T4 enters the brain, it is deiodinated to T3. TBG, thyroid binding globulins; TTR, transthyretin; CSF, cerebrospinal fluid.

Table 4
Thyroid function tests during pregnancy (Larsen et al., 1998; Fantz et al., 1999)

Physiologic change	Resulting change in thyroid activity
↑ serum estrogens	↑ serum TBG
↑ serum TBG	↑ demand for T4 and T3 ↑ in total T4 and T3
↑ hCG	↓ TSH (in reference range unless hCG >50 000 IU/L) ↑ fT4 (in reference range unless hCG >50 000 IU/L)
↑ iodine clearance	↑ goiter in I^--deficient areas ↑ in dietary requirement for I^- ↓ in hormone production in I^--deficient areas
↑ type III deiodinase	↑ demand for T4 and T3 ↑ T4 and T3 degradation
↑ demand for T4 and T3	↑ serum thyroglobulin ↑ thyroid volume ↑ goiter in I^--deficient areas

deiodinase type II and increasing deiodinase type III activity (Kamarkar et al., 1993).

An important question is whether thyroid hormone is needed throughout all phases of development or there are limited windows of thyroid hormone action. These questions are important in the analysis of the effects of maternal hypo- or hyperthyroidism and hypothyroxinemia or thyrotoxicosis on the fetus, and on prematurity (Morreale de Escobar et al., 2000). In the rat model, the peak of thyroid hormone sensitivity for the brain, judging from the highest occupancy of T3 receptors would be around postnatal day 15, and the most developmental effects of thyroid hormone action in the brain appear to take place during the first three postnatal weeks (Bernal, 2003). Most thyroid hormone-regulated genes identified to date are sensitive to the hormone at different phases within the period corresponding from about prenatal day 18 to postnatal day 25. However, there is strong evidence that the rat fetal brain is under thyroid hormone control before that age and, therefore before onset of thyroid gland function (Bernal, 2003). Receptor mRNAs can be detected as early as prenatal day 11.5 (Bradley et al., 1992), and receptor protein in nuclear preparations of the whole brain is detectable around prenatal day 14 (Pérez-Castillo et al., 1985). Of course, in the absence of the fetal thyroid, maternal hormones would play an important role at these early stages of development. It is therefore important to dissect the pathways of thyroid hormone action at these early phases of development and identify the target genes mediating these actions (Dowling et al., 2000). Additionally, it is now generally accepted that there is no single critical period of thyroid hormone action on brain development, either in humans (Delange, 2000) or in animals (Dowling et al., 2000). Rather, thyroid hormone acts on a specific development process during the period that the process is active. For example, thyroid hormone effects on cellular proliferation would necessarily be limited to the period of proliferation for a specific brain area. Because cells in different brain regions are produced at different times (Bayer and Altman, 1995), the critical period for thyroid hormone action on cell proliferation would differ for cells produced at different times. Zoeller et al. (2002) said that the window of time for thyroid hormone-dependent regulation of these processes is limited to pre- and perinatal life in mammalian animals. Also, the thyroid hormone plays a role in brain development during the fetal period. It was reported that different parts of the brain are differentially sensitive to thyroid hormone at any one time during development, and that the sensitivity to thyroid hormone is controlled, in part, by local control of hormone production (Zoeller, 2004). Taken together, thyroid activity undergoes many changes during normal pregnancy including (Fantz et al., 1999, Table 4): (a) a significant increase in serum thyroxine-binding globulin, thyroglobulin, total T4, and total T3; (b) an increase in renal iodide clearance; and (c) stimulation of the thyroid by Hcg (human chorionic gonadotropin). Therefore, these changes can make diagnosis of thyroid dysfunction during pregnancy difficult. In general, the aging process is associated with a number of thyroid function changes (Latrofa and Pinchera, 2005). The fetus is affected by three pathophysiological mechanisms including fetal hypoxia, fetal acidemia and altered feto-maternal metabolism, acting individually and in combination to cause fetal compromise (Jaeggi and Roman, 2006).

2.3.2. *In hypofunction case*

Maternal thyroxine delivery to the fetus seems to be crucial in the protection of the fetus from too low T4 levels (van Wassenaer et al., 2002). A reduction or absence of thyroid hormone during brain maturation yields molecular, morphological and functional alterations in the cerebral cortex, hippocampus and cerebellum (Lee et al., 2003). Hypothyroidism during fetal and neonatal development results in delayed neuronal differentiation and decreased neuronal connectivity (Nunez et al., 1991). Generally, a lack of TH during fetal or early postnatal life is associated with specific brain damage (Mirabella et al., 2005). This includes abnormal neuronal proliferation and migration (Potter et al., 1982), decreased

dendritic densities and synaptic profiles (Legrand, 1984), impaired synaptic transmission (Gilbert and Paczkowski, 2003), and reduced myelination (Rosman et al., 1972). In support of this, the progeny of pregnant dams on low iodine diets had permanent changes in the migratory patterns of cells migrating on prenatal days 14–16 in the neocortex and hippocampus (Lavado et al., 2000). On the another hand, Ruiz deOña et al. (1988) also demonstrated the presence of increasing type II 5′-iodothyronine deiodinase activity in the fetal brain while Sampson et al. (2000) confirmed that the maternal hypothyroidism disrupts early fetal brain development. These findings led to the suggestion that thyroid hormone is necessary for normal brain development in the fetus as it is during the early postnatal period (Obregón et al., 1984; Pérez-Castillo et al., 1985). Furthermore, a lack of maternal thyroid hormones in early pregnancy may cause a reduction in brain and body growth in the fetus that, in the case of the brain, appears to be restored to normal after the onset of fetal thyroid function (Potter et al., 1986). A number of different defects have been characterized during the neonatal hypothyroidism and include (Medeiros-Neto, 1996; de Vijlder et al., 1997): (1) decreased thyrotropin responsiveness, (2) failure to concentrate iodide, (3) defective organification of iodide due to an abnormality in the peroxidase enzyme or in the H_2O_2 generating system, (4) defective thyroglobulin synthesis or transport, and (5) abnormal iodotyrosine deiodinase activity. In turn, these observations imply that the consequences of thyroid hormone insufficiency during fetal development will differ from those of thyroid hormone insufficiency during postnatal development. Disorders of neuronal migration are considered to be the major causes of both gross and subtle brain abnormalities (Rakic, 1990). Studies in animal models have identified a number of cellular migration and differentiation events in the postnatal brain that depend upon thyroid hormone (Legrand, 1984). This postnatal brain maturation requires a functioning thyroid gland in the offspring and adequate iodine nutrition for the biosynthesis of the hormone. However, what remain less clear are the sensitivity of the fetal brain to thyroid hormone and the role of maternal thyroid hormone in promoting brain development in utero. The question then becomes how does one distinguish brain defects that originate before the fetal thyroid gland acquires activity? Ausó et al. (2004) shed light on this question in a study of carefully limited deficiency of maternal thyroid hormone in pregnant rats. The duration of the thyroid deficiency was restricted to only a few days by impeding maternal thyroid function with methimazole (MMI) between embryonic days 12 and 15, before the fetal thyroid gland has significant function (gestation is about 21 days in the rat) (Forrest, 2004). This treatment reduced maternal thyroid hormone levels in the pregnant dams. Importantly, the reduction was transient and by late gestation, shortly after cessation of treatment, thyroid hormone levels had largely recovered and the consequences of the transient thyroid impairment in utero were assessed in young adult offspring at 40 days of age. In the forebrain, some histological markers were permanently altered in the somatosensory cortex and hippocampus (Forrest, 2004). The layered structure of the neocortex is formed by progressive phases of neuronal migration beginning before midgestation. In the offspring of treated dams, the migration was retarded such that significant numbers of misplaced neurons were found in deep-lying layers. The time of generation of these cells was correlated with the period of thyroid deficiency in utero by concomitant treatment with bromodeoxyuridine, which marked dividing cells at that time (Forrest, 2004). The offspring were also susceptible to audiogenic seizures, a known consequence of more chronic thyroid impairment in rodents (Van Middlesworth, 1977). It is noteworthy that the treatment caused only a modest drop in thyroid hormone levels in the dams to 70% of normal. The effects of maternal hypothyroxinemia on the cytoarchitecture of the cortex and hippocampus are permanent (Lavado-Autric et al., 2003). In general, in human and rat, the maternal hypothyroidism during pregnancy disturbs the fetal brain development, resulting in neurological deficits in offspring (Man et al., 1991; Porterfield and Hendrich, 1993; Pickard et al., 1997; Sinha et al., 1997; Evans et al., 1999; Haddow et al., 1999; Pop et al., 1999; Forrest, 2004; Mirabella et al., 2005). Moreover, children-born to pregnant women with untreated hypothyroidism during the second trimester exhibit measurable neurological deficits despite normal circulating thyroid hormone at birth (Haddow et al., 1999; Pop et al., 1999). These findings strongly suggest that thyroid hormone, perhaps of maternal origin, plays important roles in brain development before birth.

Furthermore, the administration of growth hormone, which does not cross the placenta during pregnancy, in late gestation to hypothyroid dams, can improve fetal metabolic deficits, though not consistently (Hendrich et al., 1997). These results suggest that maternal hypothyroidism induces maternal metabolic dysfunction. Indeed, body weights, tissue protein concentrations and serum glucose levels are depressed close to term in fetuses of hypothyroid dams (Morreale de Escobar et al., 1985; Porterfield and Hendrich, 1991; Hendrich et al., 1997). Placental weights are depressed in certain hypothyroid rat dam models (Hendrich and Porterfield, 1996) but normal in hypothyroxinemic dams (Pickard et al., 1993). Although reversed following the onset of fetal thyroid function, these effects occur during the critical period of blast cell proliferation and may therefore underlie the long term changes in brain development and function noted in this model (Pickard et al., 1993, 1997; Evans et al., 1999). Maternal hypothyroxinemia in human pregnancy is also associated with cognitive and motor dysfunction in offspring in the absence of change in fetal and placental weights at term (Man et al., 1991). Findings in the hypothyroxinemic rat dam model indicate that this brain dysfunction may arise from impaired brain development before active fetal thyroid hormone secretion, when both the fetus and the placenta are dependent upon the maternal circulation for their thyroid hormone supply (Evans et al., 1999). Severe hypothyroxinemia has been associated with increased morbidity and long-term disability in premature infants (Den Ouden et al., 1996; Reuss et al., 1996). The abnormal brain development observed during hypothyroidism may, in part, result from absence of growth hormone (Savard et al., 1984). On other hand, there are three types or combinations of thyroid

deficiency states known to impact fetal development (Xue-Yi et al., 1994; Glinoer, 1997; Oppenheimer and Schwartz, 1997; Haddow et al., 1999): (1) isolated maternal hypothyroidism; (2) isolated fetal hypothyroidism (sporadic congenital hypothyroidism); and (3) iodine deficiency-combined maternal and fetal hypothyroidism. When MMI is administrated orally in drinking water to pregnant rats, the drug crosses the placenta readily, achieving a fetal/maternal blood ratio of close to 1.0 (Marchant et al., 1997).

2.3.3. *In hyperfunction case*

In early reports, neonatal hyperthyroidism was described as a critical disease marked mainly by cardiac symptoms, poor weight gain and severe neurological manifestations (Selenkow, 1975; Wing et al., 1994; Polak, 1998; Caffrey, 2000). Fetal thyrotoxicosis is the result of thyroid-stimulating antibody transfer to the fetus in the setting of maternal Grave's disease (Jaeggi and Roman, 2006). It may present with a variety of clinical features, which include persistent sinus tachycardia, fetal hydrops, intrauterine growth restriction, goiter and fetal demise (Zimmerman, 1999). The vast majority of cases of excessive serum thyroid hormone concentration seen in pregnancy are due to the overproduction of thyroid hormones (Graves' disease, toxic nodular goiter); in the postpartum period, thyrotoxicosis may be due to exacerbation of Graves' hyperthyroidism or to the release of thyroid hormone due to an acute autoimmune injury to the thyroid tissue (postpartum thyroiditis-PPT) (Momotani et al., 1994). Furthermore, the neonatal hyperthyroidism leads to permanent decrease in pituitary reserve of TSH secretion (Varma and Crawford, 1979).

On the other hand, McDermott and Ridgway (1998) reported that thyrotoxicosis usually develops as a primary disorder of the thyroid gland. Primary hyperthyroidism is characterized by clinical symptoms and signs of thyroid hormone excess; elevated circulating free thyroxine or triiodothyronine concentrations or both, and a suppressed serum level of thyrotropin (Fig. 6). Rarely, thyrotoxicosis may result from primary TSH overproduction by the pituitary gland with secondary thyroid enlargement and hyperfunction. This is referred to as central hyperthyroidism. Taken together, there are two known causes of central hyperthyroidism (McDermott and Ridgway, 1998); (1) TSH-producing pituitary tumors (TSHomas) and (2) the syndrome of pituitary resistance to thyroid hormone (PRTH). In general, thyrotoxicosis is the syndrome resulting from an excess of circulating free thyroxine and/or free triiodothyronine (Bartalena et al., 2000; Cooper, 2003; Panzer et al., 2004). Babies likely to become hyperthyroid have the highest TSH receptor antibody titer whereas if TSH receptor antibodies are not detectable, the baby is most unlikely to become hyperthyroid (Matsuura et al., 1988). In the latter case, it can be anticipated that the baby will be euthyroid, have transient hypothalamic-pituitary suppression or have a transiently elevated TSH, depending on the relative contribution of maternal hyperthyroidism versus the effects of maternal antithyroid medication, respectively (Matsuura et al., 1988). Rarely, neonatal hyperthyroidism is permanent and is due to a germline mutation in the TSH receptor resulting in its constitutive activation (Kopp et al., 1997; Grüters et al., 1998).

In fact, the optimum levels of thyroxine are essential for neural maturation (Bernal and Nunez, 1995; Morreale de Escobar et al., 2000); hypothyroidism delays and hyperthyroidism accelerates neurodevelopmental processes (Dussault and Ruel, 1987). Thus, whether the response of the newborn brain to thyroid hormones is affected by the intensity of maternal neuronal activity?

Overall, it is observed from the above mentioned results that: (1) The maternal thyroid hormones regulate the growth and metabolism of newborns, and play a critical role in CNS development and differentiation depending on the brain region and the developmental stage. (2) The significant actions of THs during CNS development occur at the time when TH levels are lower than those in the mother and the hypothalamic-thyroid

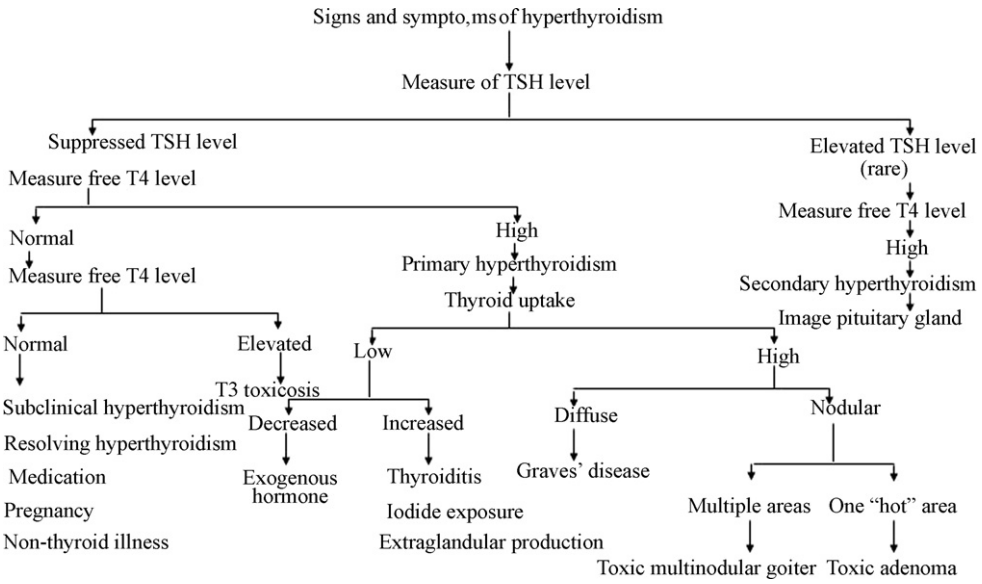

Fig. 6. Different cases of hyperthyroidism (Reid and Wheeler, 2005).

Table 5
Summary about the thyroid function in pregnancy and fetus

Thyroid function in pregnancy	Thyroid function in the fetus
(1) Pregnancy induces normal physiologic changes that affect thyroid function and thyroid function testing (Glinoer, 2004). Increased renal blood flow and glomerular filtration rate lead to an increase in the excretion of plasma iodide	(1) The fetus is able to produce thyroid hormones by 8–10 weeks' gestation, but prior to that time, is totally dependent on maternal thyroid hormones (Pop et al., 1995). By 12 weeks of gestation, active fetal iodide trapping by the fetal thyroid gland is detectable, and the ability to produce T4 occurs shortly afterward. The fetal thyroid gland becomes operational near midgestation (Glinoer, 2004). There is good evidence that transfer of maternal thyroid hormones to the fetus plays a critical role both before and after fetal thyroid functionality, because 30% of T4 levels found in cord blood are of maternal origin (Wier and Farley, 2006)
(2) During pregnancy, there is an increase in total T3 and total T4 due to increased TBG concentrations (attributed to decreased plasma clearance of TBG). This happens early, and TBG concentrations double by 16–20 weeks' gestation. Increased plasma volume, along with increased TBG, results in an increased production of total T4. By 4–6 weeks postpartum, serum TBG, T4, and T3 return to prepregnancy levels (Wier and Farley, 2006)	(2) T4 is transferred via the placenta and has been found in the gestational fluid sac of the 4–6-week-old fetus. Because of the low thyroid-binding properties of fetal fluid, the fetal free T4 levels are an important source of thyroid hormone and represent one third that of maternal free T4. Thyroid hormone is critical for normal fetal brain development: neuronal multiplication, migration, and structural organization (Wier and Farley, 2006). These processes occur mainly during the second trimester when the fetus is primarily supplied with maternal thyroid hormones (Glinoer, 2004). Brain development from the beginning of the third trimester involves glial cell multiplication, migration, and myelinization using primarily the fetal supply of thyroid hormone
(3) At the end of the first trimester, up to one fifth of euthyroid pregnant women will exhibit a small and transient increase in free T4 levels and a partial TSH suppression. During the remainder of the pregnancy, serum TSH levels should return to the generally accepted normal range of 0.4–4.0 mIU/L (Wier and Farley, 2006)	(3) A lack of adequate maternal thyroid hormone may have irreversible effects on the fetus (Pop et al., 1995). It can lead to the disruption of normal brain growth and the development of brain damage, manifesting itself in a variety of ways, such as poor cognitive development, mental retardation, and cerebral palsy (De Escobar et al., 2000, Reuss et al., 1996)

axis is not fully functional. (3) A transient and moderate deficiency or increased of maternal thyroid hormone during pregnancy can have deleterious consequences on brain morphology in the offspring.

2.4. Summary about the thyroid function in pregnancy and fetus

See Table 5.

2.5. Summary about the thyroid function and development in rodents and humans

See Table 6.

2.6. Summary about the major findings from studies performed with experimental animals, and their possible relevance for man (Morreale de Escobar et al., 2000)

See Table 7.

2.7. General comparison between the information obtained in experimental animals before onset of fetal thyroid function (BO-FTF) and after onset of fetal thyroid function (AO-FTF) (Table 8); when fetal thyroid function (FTF) starts, considering as such the onset of secretion of iodinated hormones

See Table 8.

3. Thyroid hormones, cytoskeleton and brain development interactions

Thyroid hormones are necessary for normal cytoskeletal assembly and stability and the cytoskeletal system is essential for migration and neuronal outgrowth (Porterfield, 2000). The cell's cytoskeleton was one of the first choices as a target for thyroid hormone action (Rabie et al., 1977, 1979; Nunez, 1984) because of its central role in defining the architecture and motility of the cell. Analysis of microtubule polymerization in the developing cerebellum revealed that the expression of the tau family of microtubule-associated protein and at least fiveforms of tubulin were regulated by thyroid hormone. It is still not clear whether these changes in transcript abundance are due to a direct action on gene expression, are mediated by other genes, or are regulated by post-transcriptional mechanism (Aniello et al., 1991; Nunez et al., 1991). Microfilaments are the other major component of the cell's cytoskeleton and are composed of fibrils and fiber bundles of polymers of the mechano-chemical protein actin. Both T4 and rT3 dynamically regulate actin polymerization in astrocytes by a nongenomic process (Farwell and Leonard, 1992). It is this ability of thyroid hormone to reorganize the actin cytoskeleton in the developing cerebellum rapidly that provides a key component of a nongenomic process capable of regulating neuronal migration. *In vivo*, the actin fibers used for pathfinding and guidance of the migrating neurite/growth cone during neuronal maturation are disassembled in the cerebellum of neonatal hypothyroid rats (Dodd and Jessel, 1988; Tessier-Lavigne and Goodman, 1996;

Table 6
Summary about the thyroid function and development in rodents and humans

Humans—thyroid development	Rodents—thyroid development
Similarities	
(1) The production and function of thyroid hormones are similar in rodents and humans and are controlled through physiologic feedback mechanisms and these hormones modulate lipid, carbohydrate, and protein metabolism and oxygen consumption by cells (Larsen and Ingbar, 1992; Martini, 1998)	
(2) In rodents and humans, follicles in the normal thyroid gland are filled with thyroglobulin, a glycoprotein that is one of the starting molecules for thyroid hormone synthesis (Jahnke et al., 2004). Epithelial cells of the thyroid follicle, which have a sodium iodide symporter, take up iodide from the blood. Once inside the thyroid epithelial cell, iodide is transported to the apical plasma membrane, and thyroid peroxidase, an integral membrane enzyme, catalyzes sequential reactions in thyroid hormone production. Thyroid peroxidase first oxidizes iodide to iodine and then iodinates tyrosines on thyroglobulin to produce monoiodotyrosine and diiodotyrosine, and finally links two iodinated tyrosines to produce T4 and T3 (Jahnke et al., 2004)	
(3) The thyroid gland in rats and humans produces 10–30 times more T4 than T3, the latter of which is the primary biologically active form (Jahnke et al., 2004). T3 released by the thyroid gland accounts for approximately one-tenth of the T_3 in peripheral tissues. The balance of T3 is produced from T4 through deiodinase activity	
(4) Type I and type II deiodinases convert T4 to T3, and type III inactivates T3 and T4 to 3,3′-diiodothyronine (T2) and 3,3′,5′-triiodothyronine (reverse T3, or r T3), respectively (Jahnke et al., 2004). In the adult human and rat, tissues with high levels of T3 are the brain, pituitary gland, thyroid gland, liver, and kidney	
Differences	
(1) Humans are born with a full maturation of thyroid system (Jahnke et al., 2004). Thyroid hormone synthesis does not begin until 10–12 weeks of gestation in humans (Porterfield and Hendrich, 1993). Development of the human thyroid gland begins in the third week of gestation (Fisher, 1997)	(1) Rats are born with a less developed thyroid system (Jahnke et al., 2004). The full maturation of thyroid system function is complete by 4 weeks after birth (Fisher and Klein, 1981). Thyroid hormone synthesis does not begin until 17 days of gestation (GD)17 in the rat (Porterfield and Hendrich, 1993). The developing rat thyroid gland is first visible on GD9 as an endodermal thickening in the primitive buccal cavity (Kaufman and Bard, 1999)
(2) By GD70, the thyroid gland is well developed; it begins concentrating iodide and producing thyroid hormone at this time (Shepard, 1967). TBG, the precursor protein upon which thyroid hormone is produced and stored, is present as early as GD29 in thyroid follicle cells (Fisher, 1997). As the thyroid follicle cells mature, TBG levels are detected in fetal serum by gestation week 11 and increase through gestation (Thorpe-Beeston et al., 1992)	(2) The thyroid gland is well developed and positioned in the fetal thyroid gland contains TBG and is capable of concentrating iodide (Jahnke et al., 2004). *In vitro* cultures of rat thyroid indicate its ability to synthesize thyroid hormone at least as early as GD20 (Shepard, 1967)
(3) The total (free and bound-to-serum protein) levels of maternal T4 and T3 increase during pregnancy to meet increased demand, while the maternal level of free T4 remains constant (Contempré et al., 1993; Kaplan, 1994)	(3) The total T4 and T3 concentrations in rat fetuses increase dramatically from GD18 until birth because of maturation of hormone synthesis of the fetal thyroid gland (Fisher et al., 1976; Obregón et al., 1984)
(4) During pregnancy, there is increased peripheral metabolism of free thyroid hormone; the pool of serum protein-bound thyroid hormone also increases during this time to maintain the proper level of free hormone (Glinoer and Delange, 2000)	(4) Versloot et al. (1998) demonstrated that even marginal maternal iodide deficiency decreases the availability of T4 for the fetus in the rat. Normal maternal serum T4 levels are essential to the maintenance of fetal serum T4 available for local conversion to T_3 (Calvo et al., 1990)
(5) The maternal thyroid hormones can produce neonatal thyroid hormone levels approaching the low normal level in congenitally hypothyroid children with a complete inability to synthesize thyroglobulin and therefore thyroid hormones (Vulsma et al., 1989). Maternal-embryo transfer of thyroid hormones has been detected in embryonic coelomic fluid (total T4 = 961 ± 193 pmol/L or 747 ± 150 pg/mL; total T3 = 33 ± 13 pmol/L or 18.5 ± 7.3 pg/mL) and amniotic fluid (20 ± 5 pmol/L or 16.0 ± 3.8 pg/mL; total T3 was below the detection limit of the assay at 5–11 weeks of gestation (Contempré et al., 1993)	(5) At the time of birth, as much as 17.5% of the thyroid hormones found in the newborn are of maternal origin in rats (Morreale de Escobar et al., 1990). Maternal transfer of thyroid hormone to the embryo/fetus has been verified in the laboratory rat. Thyroid hormone is detected in rat embryotrophoblasts as early as GD9 (total T4 = 4.46 ± 1.04 ng/100 mg and total T3 = 0.18 ± 0.02 ng/100 mg (Morreale de Escobar et al., 1985). Woods et al. (1984) reported that rat embryotrophoblasts (GD9–10) contained 21% of the T4 and 54% of the T3 of the maternal dose of radiolabeled T4 or T3 1 hr after administration

Table 6 (*Continued*)

Humans—thyroid development	Rodents—thyroid development
(6) TSH is first detected in the fetal human pituitary by 10–12 weeks of gestation (Fisher et al., 1976)	(6) Pituitary TSH mRNA expression begins on GD15 (Rodríguez-García et al., 1995), while TSH protein levels are first reported at GD17 measuring 24.8 ± 2 ng/pituitary (Oliver et al., 1980)
(7) Fetal serum levels reach peak concentrations around gestation weeks 22–30, and then decrease slightly until birth (Fisher et al., 1976; Roti, 1988). The decrease in TSH before birth is thought to be, in part, in response to the onset of the negative feedback system of the maturing hypothalamic–pituitary–thyroid system (Jahnke et al., 2004)	(7) The levels of pituitary and serum TSH slowly decrease from postnatal day (PND) 14–16 until reaching adult levels at PND-40 (Dussault and Labrie, 1975)
(8) TRH is detected in fetal whole-brain samples by 4.5 weeks of gestation (Winters et al., 1974). The levels of TRH detected this early are likely of maternal origin, as the fetal hypothalamus is just beginning to develop and maternal TRH is able to cross the placental barrier (Fisher, 1997). TRH is detected in fetal hypothalamus extracts as early as 8–11 weeks of gestation (Winters et al., 1974; Aubert et al., 1977). The hypothalamic–pituitary–thyroid axis begins to mature during the second half of gestation (Fisher et al., 1976)	(8) TRH mRNA can be detected as early as GD14 in neurons of the rat fetal hypothalamus (Burgunder and Taylor, 1989). By GD15, TRH mRNA is detected in the developing paraventricular nuclei of the hypothalamus (Jahnke et al., 2004) and at birth, TRH mRNA was detected in all areas of the brain known to express it in adulthood. Adult TRH mRNA expression patterns are present by PND22. TRH is produced in low levels (6.0 ± 0.5 pg/mg) in the rat hypothalamus as early as GD16 and increases approximately threefold by GD20 (Shambaugh et al., 1983). TRH levels increase to adult levels by PND17–29, then decrease transiently between PND31–41; adult levels are once again reached at PND50 (Oliver et al., 1980)
(9) The fetal pituitary can respond to TRH as early as 25 weeks of gestation; this is evidenced by an increase in fetal TSH secretion upon maternal administration of TRH, as measured by a cordocentesis procedure on normal pregnancies during 25–37 weeks of gestation (Thorpe-Beeston et al., 1992)	(9) Although TRH is present in the hypothalamus in late gestation, it does not appear to influence the hypothalamic–pituitary–thyroid axis until the second week of postnatal life (Fisher et al., 1976)
(10) The serum half-life of T4 and T3 in normal human adults is 5–9 days and 1 day, respectively, (Jahnke et al., 2004)	(10) The serum half-life of T4 and T3 in normal human adults is 5–9 days and 1 day, respectively, (Jahnke et al., 2004)
(11) Thyroxine-binding globulin is the major binding protein (Kaneko, 1989)	(11) Albumin is the major binding protein (Kaneko, 1989). Thyroxine-binding globulin, in the adult rat plays a role, leading to increased availability of T4 for metabolism and elimination, for example, deiodination (Döhler et al., 1979). The higher rate of thyroid hormone production in rodents is proposed to play a role in species differences in follicle morphology (Hill et al., 1998)
(12) Approximately 80% of T3 production in humans are from extrathyroidal deiodinase activity (Bianco et al., 2002)	(12) Approximately 80% of T3 production in humans are from extrathyroidal deiodinase activity (Bianco et al., 2002)
(13) The hypothalamic–pituitary–thyroid axis develops prenatally-from the 4th to 5th weeks through the 30th and 35th weeks of gestation (Jahnke et al., 2004)	(13) Function of the hypothalamic–pituitary–thyroid axis begins at birth and is complete by 4 weeks of age (Jahnke et al., 2004)
(14) Hypothyroidism in adult female humans is associated with: (a) Altered menstrual and estrous cycles and interference with gestation, usually during the first trimester of pregnancy (Fisher and Brown, 2000; Krassas, 2000) (b) Increased abortions and stillbirths are noted (Fisher and Brown, 2000; Krassas, 2000)	(14) Hypothyroidism in adult female rats is associated with: (a) Altered menstrual and estrous cycles and interference with gestation, usually during the first half of pregnancy (Fisher and Brown, 2000; Krassas, 2000) (b) Increased resorptions, stillbirths, and reduced litter sizes are observed (Fisher and Brown, 2000; Krassas, 2000)
(15) Hyperthyroidism in adult female humans does not affect onset of menses (Jahnke et al., 2004)	(15) Hyperthyroidism in adult female rats delays the estrus (Jahnke et al., 2004)

DL and Galton, 1997), and this defect can be repaired by single injection of thyroxine (Faivre-Sarrailh and Rabie, 1988). Total cellular actin levels do not change with thyroid status; only the relative proportions of polymers (fibrous) actin to monomeric actin are influenced by T4 (Leonard and Farwell, 1997). A second component of a nongenomic regulatory process that can directly impact neuronal migration is derived from the fact that neuronal migration/neurite guidance is directed by external cues from the extracellular matrix (ECM) protein laminin. Laminin is a product of astrocytes that is held in polymer arrays on the astrocyte cell surface by specific transmembrane receptors composed of integrin subunits. These integrin receptors cluster to form focal contacts that are anchored in place by actin filaments that bind to their cytoplasmic tails (Stitt et al., 1991; Colognato et al., 1999), and integrin clustering is necessary to anchor laminin arrays on the cell surface. T4 regulates the organization of microfilaments in both astrocytes and neurons, especially those in neuronal processes, *in vitro* and *in vivo* (Farwell et al., 2005). One important consequence of loss of the microfilaments in the developing cerebellum of hypothyroid neonates is the temporal disruption of laminin deposition ~7–10 days (Farwell et al., 1996; Farwell and Dubord-Tomasetti, 1999). T4 replacement, given at least 1 day prior to the critical time period for granule cell migration (~7–10 days after birth), normalizes the timing and topological complexity of laminin deposition and, thereby, facilitates the

Table 7
Summary about the major findings from studies performed with experimental animals, and their possible relevance for man

Cases	Experimental animals	Man
(1) Before onset of fetal thyroid function (BO-FTF)		
(A) T4 and T3 present in embryonic and fetal fluids and tissues	-Rat (Sweney and Shapiro, 1975; Obregón et al., 1986; Woods et al., 1984) -Chicken (Prati et al., 1992) -Salmon (Tagawa and Hirano, 1987) -Sheep (Ferreiro et al., 1988)	-Shown (Myant, 1958; Calvo et al., 1993; Contempré et al., 1993)
(B) T4 and T3 are of maternal origin	-Rat (Morreale de Escobar et al., 1985) -Chicken (Prati et al., 1992) -Salmon (Tagawa and Hirano, 1987)	-Supported by correlation of T4 in extra-embryonic cavity with maternal serum T4 (Contempré et al., 1993)
(C) Nuclear receptors for T3 are found, and partly occupied by T3	-Rat (Pérez-Castillo et al., 1985; Ferreiro et al., 1990; Mellström et al., 1991; Bradley et al., 1992, 1994) -Chicken (Forrest et al., 1990, 1991) -Sheep (Ferreiro et al., 1987)	-Shown (Bernal and Pekonen, 1984; Pickard et al., 1998)
(D) D2 and D3 are expressed in brain	-Rat (Ruiz deOña et al., 1988) -Chicken (Valverde et al., 1993)	-Shown (Porterfield and Hendrich, 1993)
(E) Adverse cerebral effects of low maternal T4 early in pregnancy are being reported	-Rat (Lucio et al., 1997; Dowling et al., 2000; Lavado et al., 2000) - Sheep (Porterfield and Hendrich, 1993; Sinha et al., 1992)	-Supported by epidemiological and clinical studies, and an *in vitro* study (Pal et al., 1997)
(2) Between onset of FTF and birth		
(A) Maternal transfer continues and contributes to fetal extrathyroidal thyroid hormone pools	-Rat (Morreale de Escobar et al., 1989; Calvo et al., 1990; Morreale de Escobar et al., 1990)	-Strongly suggested by earlier studies (Fisher et al., 1964; Raiti et al., 1967; Dussault et al., 1969)
(B) Brain T3 is highly dependent on T4 and the activities of D2 and D3, not on systemic T3	-Rat (Silva and Matthews, 1984; Calvo et al., 1990; Ruiz deOña et al., 1991; Morreale de Escobar et al., 1992)	-Continuing role of T4-regulated D2, and D3, in cerebral T3 (Pavelka et al., 1997)
(C) Normal maternal levels of T4 protect the fetal brain from T3 deficiency	-Rat (Morreale de Escobar et al., 1989; Calvo et al., 1990)	-Supported by good results of early treatment with T4 of newborns with CH, born from mothers with normal T4 (Morreale de Escobar et al., 2000)
(D) Normal T3 in hypothyroxinemic mother neither prevents cerebral T3 deficiency, nor maintains T3 homeostasis.	-Rat (Escobar del Rey et al., 1986, 1987; Morreale de Escobar et al., 1989; Calvo et al., 1990; Obregón et al., 1991)	-Supported by findings in ID cretins, whose mothers have low T4, but normal circulating T3 (Morreale de Escobar et al., 2000)

orderly migration of granule neurons. Interestingly, a laminin receptor has recently been identified as a specific T4-binding protein on the cell membrane (Bergh et al., 2005), although the contribution of such binding to the organization of the ECM is unknown. Thus, by modulating the organization of the actin cytoskeleton, thyroid hormone directly regulates the deposition and organization of a key guidance cue used by migrating granular neurons.

The inability of hypothyroid neonates to show normal neuronal outgrowth is thought to be a result of abnormalities in the development of cellular cytoskeleton (Dasgupta et al., 2007) and the cytoskeleton of the neuron consists of microfilaments, microtubules and neurofilaments. Hypothyroidism alters neuronal outgrowth by altering assembly, stabilization and composition of microtubule protein. This role of thyroid hormones is most likely mediated through its action on protein synthesis (Stein et al., 1991). Perinatal thyroid hormone deficiency has been shown to decrease the delivery of cytoskeletal proteins to developing terminals via the slow component of axonal transport (Fellous et al., 1979). Such changes in formation, transport and function of components of the cytoskeleton could cause the observed impairment of neuronal process outgrowth. Moreover, thyroid hormone has been demonstrated to regulate the expression of ECM and adhesion molecules that are important for neuronal migration and development, such as tenascin-C (Alvarez-Dolado et al., 1998), neural cell adhesion molecule (N-CAM) (Iglesias et al., 1996), reelin and dab1 (Alvarez-Dolado et al., 1999), laminin and fibronectin (Trentin and Moura Neto, 1995; Calloni et al., 2001; Martinez and Gomes, 2002; Trentin et al., 2003). *In vitro*, thyroid hormone down-regulates the expression of tenascin-C in glioma cell lines, whereas *in vivo*, hypothyroidism increases both RNA and protein levels of this extracellular matrix molecule in specific areas of the rat brain, including Bergmann

Table 8
General comparison between the information obtained in experimental animals before onset of fetal thyroid function (BO-FTF) and after onset of fetal thyroid function (AO-FTF)

BO-FTF	AO-FTF
Morreale de Escobar et al. (2000, 2004) reported that:	Morreale de Escobar et al. (1992, 2000, 2004) reported that:
(1) Thyroid hormones are found in embryonic and fetal tissues well in advance of the onset of fetal thyroid function, not only in rats, but also in chick and salmon embryos	(1) Once FTF starts, maternal transfer of thyroid hormones does not stop, but continues until term and represents an important proportion of fetal thyroid hormone supply
(2) The hormones found in placenta, early embryos and membranes and embryonic cavities are of maternal origin, their concentration being related to levels of maternal circulation until FTF starts	(2) In cases of fetal thyroid failure, the amounts of maternal T4 reaching the fetal brain are enough to selectively prevent cerebral T3 deficiency of a hypothyroid fetus until the umbilical cord, and the protection afforded by the maternal transfer of hormone, is severed at birth
(3) Both T4 and T3 are available to early embryos, with very low concentrations being found when circulating concentrations in the mother are low and when this occurs, prenatal and postnatal developmental alterations can be shown	(3) Maternal T4 and T3 are not equivalent for the fetal brain, because during fetal and early postnatal development, cerebral T3 depends on its local generation from T4 (through type II 50 iodothyronine deiodinase (D2) activity), and is hardly affected by circulating T3 levels. Therefore, if the mother is hypothyroxinemic, the brain of a hypothyroid fetus is T3-deficient, even if maternal and fetal circulating T3 is normal, or actually increased
(4) Thyroid hormone nuclear receptor (TR) isoforms are also present in early rodent and chicken tissues, notably in the rodent brain with concentrations increasing during periods of very active cortical neurogenesis	(4) Fetal brain T3 levels are also protected from an excess of maternal T4. Such results suggest that over-treatment of the mother with T4 is less damaging for the fetal brain than maternal hypothyroxinemia. In contrast. there is almost no protection of the fetal brain from an excess of circulating T3
(5) The simultaneous discovery of the hormone and its nuclear receptor does not show, *per se*, that the hormone is already exerting a biological effect. Recent evidence has, however, shown clearly that maternal T4 is necessary for early neurogenesis to proceed normally (Ausó et al., 2003, 2004)	(5) It is important to realize that maternal T4 and T3 are not equivalent with regard to this preferential protection of the hypothyroid fetal brain from T3 deficiency. Without correction of the low maternal T4, normal levels of T3 in the maternal or fetal circulation have no protective effect because during fetal and postnatal development cerebral structures of the rat depend entirely on the local generation of T3 from T4 by type II 5′-iodothyronine deiodinase (D2). The activity of which is inversely related to the availability of T4. Changes in the activity of 5-iodothyronine deiodinase (D3), which inactivates both T3 and T4, also play a role
(6) Many cerebral genes sensitive to thyroid hormone deprivation have been identified, mostly in postnatal rats (Bernal and Nunez, 1995; Bernal and Guadaño-Ferraz, 1998), during a phase of brain development that corresponds to the second half of gestation and early postnatal period in man	(6) During these periods of development, the contribution of systemic T3 to the amount of T3 in fetal cerebral structures is negligible. Fetal brain T3 levels are also protected from excessive maternal circulating T4, whereas cerebral T3 homeostasis is not ensured when maternal circulating T3 is excessive. Such results suggest that over-treatment of the mother with T4 is potentially less damaging for the fetal rat brain than maternal hypothyroxinemia
(7) The few studies reporting biological effects in the fetal rat brain at a phase of development corresponding to the first half of pregnancy in man have been restricted to a period coinciding or following onset of FTF at 17.5–18 days of gestation (Vega-Nuñez et al., 1995; Martinez-Galán et al., 1997; Alvarez-Dolado et al., 1999)	
(8) There is, however, increasing evidence that maternal thyroid hormone is already needed before onset of FTF; maternal hypothyroidism, as induced by treatment with goitrogens or thyroidectomy, interferes with the normal proliferation of some neurons usually completed by embryonic day 12 (Narayanan and Narayanan, 1985). It also affects the migration of cells proliferating at days 14–15, normally reaching layer VI of the cortex by days 16–17 (Lucio et al., 1997), and the cortical expression of several genes by day16 (Dowling et al., 2000). Directly related to the possible role of maternal hypothyroxinemia without hypothyroidism is finding that an altered early migration of cortical cells can be observed in offspring of rats with severe iodine deficiency (ID) (Lavado et al., 2000). These dams have very low circulating T4, but circulating T3 is high enough to prevent "clinical" hypothyroidism	

glia of the cerebellum, in early postnatal life (Alvarez-Dolado et al., 1998). In addition, thyroid hormone regulates the expression of laminin in the developing rat cerebellum (Farwell and Dubord-Tomasetti, 1999), and of fibronectin in the midbrain but not in the cerebral hemispheres of newborn rats (Calloni et al., 2001). Generally, hypothyroidism alters the neuronal cytoskeleton and neuronal growth either by affecting the developmental programs for expression of specific isoforms

of cytoskeletal proteins or by changing the delivery of cytoskeletal proteins via slow axonal transport (Stein et al., 1991).

Additionally, in light, T3 increased melatonin levels in pineal and medium of cultures from either young or maturing animals and in dark decreased melatonin levels in the pineals of either age, but was without significant effect on levels in the medium (Catala et al., 1988). Since it is known from other work that 14-day-old rat pineal glands do not yet have a complete sympathetic innervation system, it is here doubly evident that T3 can modulate directly pineal synthesis and release of melatonin, and may not depend upon a mature sympathetic innervation. Light in the studied conditions was permissive from the stimulatory action of T3 on pineal synthesis and release of melatonin *in vitro*. On the other hand, thyroid hormone is required for the normal development of the mammalian brain where it regulates a diverse set of developmental programs that include: (1) cell proliferation and migration, (2) apoptosis, (3) neuronal integration, and (4) dendritic arborization (Anderson et al., 2003; Kilby, 2003; Koibuchi et al., 2003; Zoeller and Rovet, 2004). The window of time for thyroid hormone-dependent regulation of these processes is limited to pre- and perinatal life in rodents (Leonard and Farwell, 2006). The neural cell development includes specific events such as neuronal growth, synaptogenesis, development of electrical activity, specification of neurotransmitter secretion, and myelinogenesis (Takeuchi et al., 1998).

There are some differences in the pattern of neuronal growth between animal species. For example in humans, guinea pigs and rabbits, neuronal differentiation occurs prenatally, while in others, such as rats and mice, it occurs postnatally (Timiras and Nzekwe, 1989). Also, the processes of axonal and dendritic growth, synapse formation, myelination, cell migration, and proliferation of specific populations of cells, such as the glial cells and certain late arising neurons, all occur late in brain development and are regulated by thyroid hormone (Gould et al., 1991; Bernal and Nunez, 1995; Oppenheimer and Schwartz, 1997; Rodriguez-Pena, 1999; Durand and Raff, 2000; Koibuchi and Chin, 2000). These hormones are essential for normal human brain development during a critical period beginning in utero and extending through the first 2 years postpartum (Porterfield, 2000). They regulate neuronal proliferation, migration, and differentiation in discrete regions of the brain during definitive periods. Based on the above reports, it is easy to imagine that thyroid hormone plays an important role in developmental processes such as neuronal proliferation that occur in different brain areas at different times (Bayer and Altman, 1995). Therefore, the temporal ''window'' of thyroid hormone sensitivity will depend on the developmental period over which a particular process occurs, and this will differ for different brain areas and thyroid hormone deficiency during a critical developmental period can impair cellular migration and development of neuronal networks (Zoeller and Crofton, 2000). Neuronal outgrowth and cellular migration are dependent on normal microtubule synthesis and assembly and these latter processes are regulated by thyroid hormones (Nunez et al., 1991). Neuronal migration is an essential step in the genesis of the nervous system, particularly in laminated brain regions (Marín-Padilla, 1971; Rakic, 1988, 1990; Hatten, 1993). Furthermore, dendritic spines are sites of synaptic connections; dendritic changes may thus directly affect synapse number and formation, and thereby underlie cognitive deficits (Thompson and Potter, 2000). On the other word, the oligodendrocyte is a well-recognized target of thyroid hormones in the developing brain and these hormones regulate oligodendrocyte production of myelin (Anderson, 2001). Thyroid hormone also plays an additional role in oligodendrocyte development by controlling proliferation of the oligodendrocyte precursor cell; the oligodendrocyte type II astrocyte (O-2A) (Durand and Raff, 2000). Moreover, astrocyte cells clearly play a role in neural development, but nowadays their total action is seen as a far wider one (Anderson, 2001) and recent findings consider them as stem cells, involved in the control of most facets of functional neural networks. Astrocytes play a central role in thyroid hormone metabolism in the brain, being the principal transporters of thyroxine from the blood, responsible for its conversion to 3,5,3′-triiodothyronine and hence supplying the neural tissues with the biologically active form of the hormone and specific thyroid hormone transporters play an essential role in this regulatory system (Anderson, 2001). The presence of thyroid hormone receptors has been demonstrated in cultured astrocytes. Furthermore, thyroid hormone regulates several aspects of astrocyte differentiation and maturation, including the production of extracellular matrix proteins and growth factors, and thus controls neuronal growth and neuritogenesis (Anderson, 2001). Therefore, astrocytes are currently suggested as important mediators of thyroid hormone in neuronal development and astrocytes play a myriad of roles in normal brain function. *In vitro*, thyroid hormone has been demonstrated to regulate actin polymerization and the extracellular organization of laminin in astrocytes (Siegrist-Kaiser et al., 1990; Farwell and Dubord-Tomasetti, 1999). These effects are postulated to play roles in neural migration. Thyroid hormone has also been demonstrated to induce the proliferation of astrocytes *in vitro* (Trentin and Moura Neto, 1995). The majority of free T3 found in the brain is locally produced by astrocytes and that D2 activity provides a level of thyroid hormone action control by increasing its activity when T4 levels are low (Anderson, 2001). This mechanism may thus ensure stable levels of brain T3 concentrations in the face of fluctuations in thyroxine production (Larsen et al., 1998). In contrast, type I iodothyronine 5′-deiodinase, the primary peripheral deiodinase, is downregulated in peripheral tissues during hypothyroidism, perhaps evolving as a mechanism to protect peripheral tissues from T4 depletion during hypothyroidism. Astrocytes may also play a role in T4 transport across the blood–brain barrier, although the mechanism of T4 transport into the brain is not yet clear (Dratman and Gordon, 1996; Bernal, 1999). Also, we can show a different types of deiodination on astrocyte cells as a following:

(1) *D1*: Astrocytes seem not to contain type I deiodinase (D1), the enzyme that converts the inactive rT3 to T2. Moreover, the production of sulfates (3,3′-T2 sulfate, T2-S, and 3′-T1 sulfate, T1-S), but not glucuro-conjugates, by T3-treated

astrocytes in culture has been demonstrated. T2-S is a major T3 metabolite produced by these cells (Esfandiari et al., 1994a).

(2) *D2*: Astrocyte D2 is a very short-lived enzyme, dynamically regulated by both T4 and 3,3′,5′-triiodothyronine, but not T3. T4 down-regulates the levels of D2 in astrocytes in a process that involves the enzyme's internalization (Siegrist-Kaiser et al., 1990). Myosin 5a is responsible for the binding of primary endosomes to the microfilaments, promoting actin-based endocytosis of D2 (Stachelek et al., 2000, 2001). D2 ubiquitination is accelerated by T4 catalysis and thus maintains local T3 homeostasis and reversible ubiquitination rescues D2 from irreversible proteolysis and regulates the supply of active thyroid hormone in D2-expressing cells (Bianco et al., 2002; Bianco, 2004; Bianco and Larsen, 2005).

(3) *D3*: Astrocytes also express D3, a selenoprotein that is responsible for the degradation of thyroid hormone in the brain (Ramauge et al., 1996). The opposing activities of D2 and D3 are believed to maintain brain T3 levels (Santini et al., 2001). In astrocytes, multiple pathways induce D3 including cyclic adenosine monophosphate (cAMP), 12-*O*-tetradecanoylphorbol-13-acetate (TPA), fibroblast growth factors (FGF), thyroid hormones and retinoic acid (Courtin et al., 1991; Esfandiari et al., 1994b).

Pretaining to the normal neurological development, the thyroid hormones act in the following manner (Porterfield, 1994): (a) They increase the rate of neuronal proliferation in the cerebellum (Dussault and Ruel, 1987). (b) They act as the "time clock" to end neuronal proliferation and stimulate differentiation (Dussault and Ruel, 1987; Pasquini and Adamo, 1994). (c) Once neurons are formed, they follow an orderly pattern of migration to the appropriate areas in the brain. This is particularly apparent in the cerebral and cerebellar cortex (Çalikoğlu, 1999). (d) They stimulate the formation and development of neuronal processes—both axons and dendrites (Klein et al., 1972). (e) Development of neuronal processes leads to formation and development of synapses. Neuronal outgrowth requires an intact functional cytoskeleton; thyroid hormones are important for normal formation, function, and stability of this cytoskeletal system (New England, 1985; Rovet et al., 1987). (f) In the absence of thyroid hormones, myelinization is delayed, as is the normal biochemical maturation of neurons (Fisher and Klein, 1981). In the rat brain, Oppenheimer and Schwartz (1997) depicted that TH influences developmental processes in multiple brain regions during a critical developmental period (first three postnatal weeks).

It is apparent from the pre-said studies that the processes of axonal and dendritic growth, synapse formation, myelination, cell migration, and proliferation of specific populations of cells, such as the glial cells and neurons, all occur during the brain development and are regulated by thyroid hormones. Overall, Table 9 follows the importance of the cytoskeleton as a target for thyroid hormones in the brain (Leonard and Farwell, 2006), while Bernal (2003) speculated the role of thyroid hormones on normal brain development as in Table 10.

Table 9
The importance of the cytoskeleton as a target for thyroid hormones in the brain

(1) Early development of the cerebellum
(a) Components of the microtubules, tubulin and microtubules associated proteins (MAPs), show hormone-dependent changes in transcript and protein abundance
(b) The organization of actin fibers are regulated by thyroid hormone
(c) Cell migration requires an intact cytoskeleton
(2) Astrocyte function
(a) The actin polymerization is regulated by thyroid hormone
(b) Integrin receptor clustering requires an intact actin cytoskeleton
(c) Laminin deposition on the astrocyte cell surface is regulated by thyroid hormone

Table 10
The role of thyroid hormones on normal brain development

(1) Early embryonic brain development:
(a) No effects on neural induction, neurulation, and establishment and polarity and segmentation
(2) Cell migration and the formation of layers:
(a) Cerebral cortex: contributes to the right position of neocortical neurons, and therefore to the normal layering pattern, and to the distribution of callosal connections
(b) Cerebellum: controls the rate of migration of granular cells from the external germinal layer to the internal granular layer. In addition, the timing of this migration in the developing cerebellum is regulated by thyroid hormone (Farwell et al., 2005)
(3) Neuronal and glial cell differentiation:
(a) Specific neuronal types:
(i) Controls dendritic development and number of dendritic spines of pyramidal cells of neocortex and hippocampus. Dendritic spines are important in synaptic plasticity
(ii) Influences differentiation of cholinergic cells of brain stem and forebrain
(iii) Maturation of dendritic arborization of Purkinje cells: in the absence of thyroid hormone, Purkinje cells have elongated primary dendrite, reduced dendritic arborization and persistence of transient axo-somatic connections
(b) Oligodendrocyte differentiation:
(i) T3 is an instructive factor for oligodendrocyte differentiation from stem cells
(ii) Thyroid hormones are required for normal myelination. Hypothyroid rats display transiently reduced expression of myelin genes and permanently reduced number of myelinated axons

4. Hypothyroidism and brain development interactions

Several reports are listed on the harmful effect of thyroid hormone deficiency during the development (Nicholson and Altman, 1972a; Lauder, 1977a,b; Stein et al., 1991; Porterfield and Hendrich, 1993; Bernal and Nunez, 1995; Oppenheimer and Schwartz, 1997; Anderson, 2001; Wong and Leung, 2001; Lavado-Autric et al., 2003; Lee et al., 2003; Farwell et al., 2005; Koibuchi, 2006; Stoica et al., 2007). Taken together, hypothyroidism can be classified based on its time of onset (congenital or acquired), severity (overt {clinical} or mild {subclinical}), and the degree of endocrine aberration (primary or secondary) (Roberts and Ladenson, 2004). Primary hypothyroidism follows a dysfunction of the thyroid gland itself, whereas secondary hypothyroidism results from the

dysfunction of metabolic or messenger pathways associated with thyroid hormone production and metabolism (Kirsten, 2000; Shagum, 2001; Guha et al., 2002). Primary hypothyroidism is characterised by reduced free thyroxine (FT4) levels and elevated thyroid-stimulating hormone levels (Brown et al., 2005). Also, the most prevalent cause of central hypothyroidism is a defective development of the hypothalamus or pituitary leading to multiple pituitary hormone deficiencies, while defects of hypothalamic and pituitary peptides and their receptors only rarely have been identified as the cause of central congenital hypothyroidism (Grueters et al., 2002). Hypothyroidism, generally, is the most common pathological hormone deficiency (Roberts and Ladenson, 2004).

Many studies have characterized the neuroanatomical consequences of developmental hypothyroidism. Early work by Eayrs demonstrated that perinatal hypothyroidism could alter the density and size of neuronal perikarya within specific brain regions, as well as fibre density and orientation within adult cortical layers (Eayrs and Taylor, 1951; Eayrs, 1955; Eayrs and Horne, 1955). Additionally, Berbel et al. (1993, 1994, 1996, 2001) have published a series of studies characterizing the effect of developmental hypothyroidism on a variety of anatomical features, including spine density of pyramidal neurones in the cerebral cortex, the organization of callosal connections, and other features. These studies have shown that hypothyroidism produces changes in callosally projecting neurones, which may be due to the maintenance of a juvenile pattern of projections. Also, thyroid hormone deficiency during a brief perinatal period produces severe neurological defects in humans and experimental animals (Thompson, 1996). During critical periods of development, hypothyroidism causes abnormalities of the CNS such as incomplete maturation of neuronal and glial cells, reduction in synaptic densities and myelin deficits (Wong and Leung, 2001). In human, thyroid hormones deficiency during the perinatal period leads to cretinism, a syndrome associated with mental retardation and neurological deficits (DeLong, 1990; Porterfield and Hendrich, 1993). In experimental animals, thyroid hormone deficiency causes an array of abnormalities in the CNS of which alterations of cell migrations are of special relevance (Alvarez-Dolado et al., 1999).

TH deficiency results in multiple morphological alterations in neonatal rat brain (Schwartz, 1983; DeLong, 1996). Cells in the cortex during hypothyroidism are smaller and more closely aggregated than normal, due in part to an overall decrease in development of axonal and dendritic processes and the axonal density is decreased and the probability of axo-dendritic interaction is reduced by an estimated 80% (Eayrs, 1960, 1971). TH deficiency also causes specific defects in cell migration and differentiation because of the regulatory effects of thyroid hormones on the processes of terminal brain differentiation such as dendritic and axonal growth, synaptogenesis, neuronal migration and myelination (Eayrs and Taylor, 1951; Eayrs and Horne, 1955; Eayrs, 1955). On the other hand, cell migration is known to be altered by hypothyroidism in the neonatal cerebellum (Legrand, 1984). Furthermore, thyroid hormone deficiency during fetal and neonatal periods in rats produces deleterious effects, such as reduced synaptic connectivity, delayed myelination, disturbed neuronal migration, deranged axonal projections, decreased synaptogenesis and alterations in levels of neurotransmitters (Geel et al., 1967; Dussault and Ruel, 1987; Oppenheimer and Schwartz, 1997). In addition, a lack of thyroid hormone in the postnatal period causes an irreversible mental retardation, characterized by a slowing of thoughts and movements accompanied by prolonged latencies of several evoked potentials and slowed electroencephalographic rhythms (Hoffmann and Dietzel, 2004).

On the other hand, the 50-day-old rehabilitated rats (beginning at postnatal day 25 by withdrawal of the propylthiouracil (PTU) from the drinking water) showed increased locomotor activity both in running-wheel and in hole-board tests; this hyperactivity, though markedly reduced, still persisted at day 90 (Tamasy et al., 1986b). Also, in the early phase of rehabilitation (50 days of age), decreases in exploratory activity and lack of habituation occurred with the hole-board test; by the late phase of rehabilitation (90 days of age) these behavioral parameters had become normal. These results suggest generally longer periods of plasticity of the brain and better prospects for rehabilitation from neonatal cretinoid retardation than commonly believed. Specifically, the pituitary–thyroid system and neural mechanisms integrating adaptive behavior possess considerable capacity for spontaneous recovery from hypothyroidism; certain types of altered neuroendocrine and behavioral responses appear to be less amenable to rehabilitation or require longer periods for complete rehabilitation (Tamasy et al., 1986b).

As well, inhibition of thyroid hormone synthesis occurred by a group of Thioureylene drugs (methimazole, propylthiouracil (PTU), thiourea or carbimazole) can inhibit the synthesis of thyroid hormones (Fig. 7). These drugs interfere with the conversion of iodide to iodine and consequently the iodination of tyrosyl groups. The tyrosyl groups are also inhibited from joining to form T3 and T4. Hypothyroidism during the postnatal period, induced by the administration of either methimazole or PTU, is known to markedly retard both maturation and development of the nervous system (Darbra

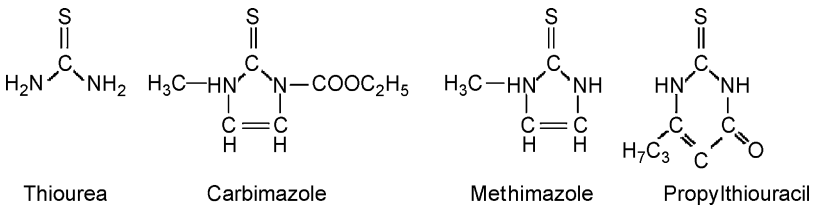

Fig. 7. Thioureylene drugs are related to thiourea (the thiocarbamide group is essential for their antithyroid activities).

et al., 2003). Moreover, PTU is an antithyroid drug that reportedly can impair olfactory function in humans and mice (Etienne et al., 2003). Also, Mookadam et al. (2004) reported that neonatal rats receiving the antithyroid drug MMI in their mothers milk are rendered hypothyroid. Another hypothyrodism drugs are summarized in Table 11 (Chiovato et al., 1997). Amiodarone-induced hypothyroidism and is easily treated by L-thyroxine replacement therapy (Martino et al., 2001). In humans, severe hypothyroidism during development results in cretinism (Legrand, 1979; Porterfield, 1994). In rodents, several neural populations have been shown to be sensitive to hypothyroidism during the pre- and postnatal periods (Koibuchi and Chin, 2000). On the other hand, L-thyroxine is considered the treatment of choice for hypothyroid patients as it has a long half-life, is inexpensive to produce and provides stable levels of T4, T3 and TSH over 24-h period (Saravanan and Dayan, 2004). At day 50, serum concentration of TSH and thyroid hormones revealed no detectable amounts of T4 and a 10-fold increase in TSH in the hypothyroid rats (0.1% PTU) a reversible antithyroid goitrogen in the litter's drinking water) (Tamasy et al., 1986a). At the same age in the hypothyroid rehabilitated animals (PTU water from birth to day 25, normal water thereafter), TSH levels were still below normal, a deficit fully normalized by day 90. Indeed, this favourable pharmacodynamic profile linked with excellent bioavailability following oral administration and the ability to fine titrate dosing using sensitive TSH assays has led most endocrinologists to believe that, unlike all other hormones, thyroid hormone replacement is straightforward (Saravanan and Dayan, 2004).

Additionally, hypothyroidism affects the migration of cells from germinative zones toward the olfactory bulb and caudate putamen region (Lu and Brown, 1977). These observations can be linked to the reduction in reelin content in the hypothyroid brain during the perinatal period (Alvarez-Dolado et al., 1999) and the abnormal expression of reelin at around birth argues against the proposed thyroid resistance of the fetal brain and clearly indicates that reelin is an early target of thyroid action during late fetal development. It is important to recognize that the results of Lavado-Autric et al. (2003) are not a case of delayed migration, but rather a case of a permanent alteration of cortical cytoarchitecture. The previous authors observed neurons in heterotopic positions at postnatal day 40. By this time, these cells would clearly be fully differentiated neurons. There is little information about the consequences that these defects in cytoarchitecture can have on the functioning of the adult rat brain, but it is very clear that migration defects in the human brain are associated with neurological deficits (Sun et al., 2002). The radial migration of cortical neurons is unique in that postmitotic neurons migrate along scaffolding provided by so-called radial glia (Hatten, 2002). However, it is unclear how thyroid hormone produces the observed effects.

Table 11
Drugs that may produce thyrotoxicosis or hypothyroidism in the elderly (Chiovato et al., 1997)

(1) Hypothyroidism
Lithium
Amiodarone
Iodide overload
Aminoglutethimide
Resorcinol
(2) Thyrotoxicosis
Amiodarone
Iodide overload
(3) Thyrotoxicosis and/or hypothyroidism
Interferon alfa
Interleukin-2
Granulocyte-macrophage colony-stimulating factor

In vivo, it has been shown that early thyroid hormone deficiency leads to impaired maturation of radial glial cells in the CAl region of the hippocampus (Martínez-Galán et al., 1997) and the Bergmann astrocytes of the cerebellum (Pesetsky, 1973). An elegant series of studies have also implicated the astrocyte in the 5′-deiodination of T4 to T3 in the brain (Anderson, 2001). The enzyme responsible for this conversion in the brain, type II iodothyronine 5′-deiodinase, is upregulated in astrocytes in the hypothyroid brain (Guadaño-Ferraz et al., 1997, 1999). Thus, TH influences the size, packing density and dendritic morphology of neurons throughout the brain. Therefore, from the pre-said studies, it is vital to overview the effects of hypothyroidism on different brain regions and iodine deficiency disorders (IDD) in details as the following in Tables 12 and 13, respectively.

Hypothyroidism in developing rat impairs synaptic transmission and has devastating effects on neurological functions that may be permanent (Gilbert and Paczkowski, 2003). Deficiencies of myelination have been observed in the cerebral cortex, visual and auditory cortex, hippocampus and cerebellum, areas which relate to the observed neurodevelopmental delay (Balázs et al., 1969; Rosman et al., 1972). All these effects in rats can be reversed by thyroid supplementation but only if supplementation is started before the end of the second week of extrauterine life (Thompson and Potter, 2000). The greater the delay in thyroid replacement the less the chance of recovery (Eayrs, 1971; Legrand, 1986). However, hypothyroid animals can maintain a close to normal level of triiodothyronine in the brain tissue for extended periods (Rudas et al., 2005). This phenomenon is due to at least three regulating mechanisms: (1) Uptake of thyroid hormones is enhanced. It was shown that the uptake by the telencephalon of labelled triiodothyronine was much higher in thyroidectomized (TX) animals than in controls or in thyroidectomized and T3 supplemented ones. (2) Conversion of thyroxine into triiodothyronine is increased. One of the most important elements of this process is the adjustment of the expression and activity of the type II deiodinase of the brain to a higher level. Enzyme kinetic studies, expression of TR-α and β-nuclear thyroid hormone receptors and after cloning the chicken type II deiodinase-*in situ* hybridization studies clearly supported the central role of the conversion process. (3) The rate of loss of triiodothyronine from the brain tissue is slowed down under hypothyroid conditions as evidenced by hormone kinetic studies (Rudas et al., 2005). Abnormal migration of neurons has been linked to cognitive deficits, mental retardation, and motor

Table 12
The effects of hypothyroidism on different brain regions

(A) Cerebrum region

(1) Deficient cellular maturation in the cerebral cortex of hypothyroid rats is characterized by (Schwartz et al., 1997; Balázs, 1973)
  (a) Smaller neuronal cell bodies that are more tightly packed than those in euthyroid animals
  (b) Diminished axonal and dendritic outgrowth, elongation, and branching
  (c) Reduced numbers of dendritic spines. Inadequate cellular differentiation results in markedly reduced synaptogenesis
  (d) Diminished myelination of neuronal axons
  (e) Changes in callosally projecting neurones, which may be due to the maintenance of a juvenile pattern of projections (Zoeller and Rovet, 2004)
  (f) Alterations in dendritic morphology and structure in several cell types, including pyramidal cells in the cortex (decrease in dendritic spine number) (Schwartz, 1983)

(2) There is retarded development of the neuropil in the cortex (Nicholson and Altman, 1972a)

(3) Also, a reduction, or absence, of thyroid hormone during brain maturation yields molecular, morphological and functional alterations in cerebral cortex (Lee et al., 2003). On the other hand, cerebral neuronal migration has been traditionally considered to be unaltered by hypothyroidism, possibly because of the fact that this process is mostly completed before birth, and also by the presumption that the fetal brain is insensitive to thyroid hormone (Schwartz et al., 1997)

(4) The neonatal hypothyroidism inhibits the development of CNS by affecting the myelination of the cerebral cortex and the maturation of neuronal circuits. This leads to permanent brain dysfunction (Wong and Leung, 2001)

(5) In general, neonatal TH deficiency includes altered dendritic structure cortical pyramidal cells (Oppenheimer and Schwartz, 1997; Thompson and Potter, 2000)

(B) Cerebellum region

The previous studies on hypothyroid rats have revealed that:

(1) The delay in migration may disrupt the precise timing required to establish productive interneuronal connections, and thus cause the decreased number and density of synaptic contacts between granule cells and Purkinje cells (Nicholson and Altman, 1972b,c; Rabie and Legrand, 1973; Legrand, 1979). Delay rather than absence of a particular cell type or process is characteristic of the hypothyroid phenotype

(2) Hypothyroid rats exhibit a persistent external granule cell layer (EGL), reduced proliferation of granule cells of rat brain in the EGL (Lauder, 1977a,b) and slowed migration of granule cells into the internal granule cell layer (IGL) (Balázs et al., 1971a,b; Nicholson and Altman, 1972b,c)

(3) Abnormal organization of the trunk of the Purkinje cell dendritic tree (dendritic arborization markedly reduced), persistent hypoplasia of the dendritic field, and a reduction in spine number (Legrand, 1967a,b; Legrand, 1984)

(4) The absence of thyroid hormone during the first postnatal weeks causes profound Purkinje cell hypoplasia (Potter et al., 2001)

(6) Marked stunting of the development of Purkinje cells (Schwartz et al., 1997)

(7) In rodents, there are a positional alterations in Purkinje cells (Alvarez-Dolado et al., 1999)

(8) In addition, ectopic localization of neonatal Purkinje cells is a typical abnormality found in the hypothyroid cerebellum, which remarkably also occurs to much higher extent in reeler mice (Legrand, 1984; Miyata et al., 1996)

(9) Anderson (2001) depicted in the hypothyroid rat cerebellum that:
  (a) A reduction in Purkinje cell dendritic arborization
  (b) A delay in granule cell migration from the EGL to the IGL and cell death is increased
  (c) A reduction in parallel fiber outgrowth and migration of the granule cells
  (d) A consequent reduction in the ultimate number of granule cells

(10) Nicholson and Altman (1972b&c) reported that hypothyroidism caused:
  (a) Decreased body, brain and cerebellar weight
  (b) Prolonged cell proliferation in the EGL and retarded disappearance of this layer
  (c) Retarded cell differentiation in the molecular and internal granular layers
  (d) Terminal increase in granule cells and astrocytes, and decrease in basket cells

(11) Also, outgrowth of the granule cell axon, the parallel fiber, is retarded in the hypothyroid cerebellum (Lauder, 1978). Further, the delay in cell acquisition and development results in abnormal proportions of all cell types found in the cerebellum, including basket cells, stellate cells, and astrocytes

(12) Diminished myelination of neuronal axons is observed in cerebellum (Schwartz et al., 1997)

(13) There is retarded development of the neuropil in the cerebellar Purkinje cells (Nicholson and Altman, 1972b,c). Neuronal bodies are smaller and more densely packed, there is diminished dendritic branching and elongation, as well as altered distribution of dendritic spines and delayed cell proliferation and migration (Nicholson and Altman, 1972b,c)

(14) Perinatal T3 deficiency leads to severe cellular perturbations, among them a striking reduction in the growth and branching of Purkinje cell dendritic arborization (Heuer and Mason, 2003). Addition of T3 to cerebellar cultures causes a dramatic increase in Purkinje cell dendrite branching and caliber in a dose- and time-dependent manner. However, One question is whether thyroid hormone acts on Purkinje cell development directly or instead acts on granule cells, and thus indirectly on Purkinje cells. To boost dendritogenesis, T3 signaling must be activated within the Purkinje cell

(15) Furthermore, *In vivo*, neonatal hypothyroidism results in an increased number of astrocytes and Bergmann glia in the rat cerebellum (Clos and Legrand, 1973)

(16) The lack of thyroid hormone during the critical period of neuronal migration leads to a multitude of irreversible morphological abnormalities (Legrand, 1979; Morreale de Escobar et al., 1983; Dussault and Ruel, 1987; Porterfield and Hendrich, 1993; Bernal and Nunez, 1995), including:
  (a) Defects in granule cell migration
  (b) Increased granule cell death (Rabie et al., 1977, 1979; Dubuis et al., 1992)
  (c) Blunted dendritic arborization of Purkinje cell (Legrand, 1979; Ruiz-Marcos et al., 1982; Vincent et al., 1982)

(17) Generally, in addition to effects on cerebellar development, TH deficiency causes alterations throughout the brain, including decreased myelination, decreased synaptogenesis, and altered morphology of multiple cell types (Potter et al., 2001)

(18) Taken together, altered thyroid status disturbed the maturation of the cerebellum and led to defects in granule cell migration, Purkinje cell arborization, the timing of apoptosis, and neuronal integration (Legrand, 1967a,b)

(19) Overall, a deficiency of thyroid hormones in the neonatal rat has been shown to cause disorganization of the cerebellar cortex (Hamburgh et al., 1971; Nicholson and Altman, 1972b,c; Nunez, 1984). In addition, a reduction, or absence, of thyroid hormone during brain maturation yields molecular, morphological and functional alterations in the cerebellum (Lee et al., 2003)

(C) Hippocampus region

(1) The effects of hypothyroidism in the hippocampus (Lee et al., 2003) include:
  (a) A reduction in the number of dentate gyrus granule cells (Madeira et al., 1991)

Table 12 (*Continued*)

(b) A decrease in pyramidal cell spine densities (Gould et al., 1990)
(c) Changes in kainate-induced gene expression (Giardino et al., 1995; Calzà et al., 1996)
(d) A decrease in the number and size of dendritic spines of Purkinje cells (Legrand, 1979)
(e) A decrease in the branching of apical and basal dendrites granule and pyramidal cells (Rami et al., 1986)

(2) Also, it has recently been shown that iodine deficiency causes an impaired maturation of hippocampal radial glial cells, which are involved in neuronal migration (Martínez-Galán et al., 1997). Specific alterations in dendritic morphology have been identified in the granule and pyramidal cells in the hippocampus due to TH deficiency (Schwartz, 1983; Rami et al., 1986)
(3) Lavado-Autric et al. (2003) reported that subtle insufficiency of thyroid hormone in the pregnant rat disrupts the migration of neurons in hippocampus, leading to the presence of neurons in aberrant locations of the adult offspring's brain and "blurring" cortical layers
(4) Perinatal hypothyroidism inhibits migration of dentate granule cells, decreases cell number, and reduces the dendritic arborization of granule and pyramidal cells (Dussault and Ruel, 1987; Gould et al., 1990; Rami and Rabie, 1990; Madeira et al., 1991, 1992; Madeira and Paula-Barbosa, 1993). Despite reestablishment of an euthyroid state upon termination of exposure, alterations in structural morphology of the hippocampus remain (Malenka et al., 1989; Madeira et al., 1992; Madeira and Paula-Barbosa, 1993)
(5) It is well established that postnatal hypothyroidism in the rat results in impaired brain development (Dussault and Ruel, 1987; Munoz and Bernal, 1997; Morreale de Escobar, 2001; Bernal, 2002). The arrival of migrating cells from the proliferative zone to the granule cell layer of the dentate gyrus is severely retarded in experimental models of perinatal hypothyroidism (Rami and Rabie, 1990)
(6) In hippocampus, deficiencies in cell acquisition, increases in neuronal death, and impaired dendritic arborization result in irreversible reductions in total granule cell number, volume of the granule cell layer, cell density and synapse number (Gould et al., 1990; Rami and Rabie, 1990; Madeira et al., 1991). Structural perturbations induced by develop mental hypothyroidism are likely to contribute to the permanent impairments in synaptic transmission reported by Gilbert and Paczkowski (2003)
(7) Abnormalities in synaptic architecture induced by thyroid hormone insufficiencies, as well as deficiencies in protein substrates involved in complex signaling pathways critical for synaptic plasticity, culminate to perturb hippocampal neurophysiological function (Gilbert and Paczkowski, 2003)
(8) Generally, altered dendritic structure of hippocampal pyramidal cells caused during the neonatal TH deficiency (Oppenheimer and Schwartz, 1997; Thompson and Potter, 2000)
(9) Finally, a reduction, or absence, of thyroid hormone during brain maturation yields molecular, morphological and functional alterations in hippocampus (Lee et al., 2003)

(E) Pituitary and auditory cortex
(1) TH regulates the synthesis and secretion of several pituitary hormones. Absence of GH has been observed in the pituitaries of hypothyroid rats (Samuels et al., 1988)
(2) An abnormal laminar distribution has been reported in the auditory cortex of hypothyroid rats, including an increased number of neurons in layers V/VI, a concomitant decrease in layers II to IV, and the abnormal presence of neurons in the subcortical white matter (Berbel et al., 1993; Lucio et al., 1997). These cytoarchitectonic abnormalities most probably reflect migration defects in the cortex
(3) Congenital hypothyrioidsm may be caused the symptom of a defective hypothalamic-pituitary development (Grueters et al., 2002)

Table 13
The spectrum of iodine deficiency disorders, IDD; adapted from Hetzel (1983) and Stanbury et al. (1998)

Fetus
Abortions
Stillbirths
Congenital anomalies
Increased perinatal mortality
Endemic cretinism
Neonate
Neonatal goiter
Neonatal hypothyroidism
Endemic mental retardation
Increased susceptibility of the thyroid gland to nuclear radiation
Child and adolescent
Goiter
(Subclinical) hypothyroidism
Impaired mental function
Retarded physical development
Increased susceptibility of the thyroid gland to nuclear radiation
Adult
Goiter with its complications
Hypothyroidism
Impaired mental function
Spontaneous hyperthyroidism in the elderly
Iodine-induced hyperthyroidism
Increased susceptibility of the thyroid gland to nuclear radiation

disorders (Eksloglu et al., 1996; Sheldon et al., 1997; des Portes et al., 1998; Gleeson et al., 1998). In addition, adult thyroid dysfunction is also associated with both neurological and behavioral abnormalities (Calzà et al., 1997); however, the mechanisms of actions thyroid hormones in the adult CNS are poorly understood. Generally, hypothyroidism during brain development results in permanent functional deficits (Schoonover et al., 2004). Hence, it is apparent from the prevoius results that thyroid hormone deficiency causes a series of abnormalities in the CNS which may lead, in turn, to an irreversible impairment, disorganization and maldevelopment. This drastic effect may be responsible for the loss of neurons vital functions. Indeed, the functional effects of thyroid hormone can be explained by identified deficits in the cellular organization observed in the hypothyroid brain.

5. Hyperthyroidism and brain development interactions

Hyperthyroidism is a hypermetabolic state accompanied by increased oxygen utilization, increased production of reactive oxygen species and consequentially measurable changes in antioxidative factors (Mayer et al., 2004). Hyperthyroidism leads to an overproduction of thyroid hormones, which determine diverse expressions of thyrotoxicosis (Wemeau, 2005). In cats, hyperthyroidism usually caused by an autonomous thyroid condition, but rarely can result from a hypothalamic or pituitary disorder (Feldman and Nelson, 1996). In addition, studies by other research workers have shown that thyroid hormone status and hyperthyroidism also lead to membrane lipid alterations (Chen and Hoch, 1976; Hoch et al., 1976, 1981; Hoch, 1977;

Pasquini et al., 1980; Fass and Carter, 1981, 1982; Ruggiero et al., 1984). On the other hand, treatment of rats with T3 resulted in a significant decrease in body weight (Katyare and Billimoria, 1989). Furthermore, neonatal hyperthyroidism (Varma and Crawford, 1979) results in: (1) permanent decrease in pituitary reserve of TSH secretion and (2) a permanent imprinting regarding growth and thyroidal development and thus, neonatal period is critical for thyroidal development. The most common causes of hyperthyroidism are Graves' disease, toxic nodular goiter, and iodine-induced hyperthyroidism and can be treated medically with antithyroid drugs or radioactive iodine, or surgically (Pearce and Braverman, 2004).

Surprisingly, however, to date, no attempt has been made to quantify thyroid hormone concentrations in the brain itself in hyperthyroidism, e.g., after its induction in euthyroid laboratory animals (Broedel et al., 2003). Some authors found either no increase in T3 concentrations in the cortex or cerebellum (van Doorn et al., 1984) or "brain" (Dratman et al., 1983) or an only 15% increase in cortical levels of T3 but a doubling of cerebellar T3 concentrations after the highest dose of 80 μg thyroxine T_4/kg body wt. of three groups of hypothyroid rats (Escobar-Morreale et al., 1995). After 8 weeks of treatment with doses of T3 and T4 that led to two- to fivefold increases in the serum concentrations of T3, the tissue levels of T3 remained unchanged in four functionally important areas (two cortical areas, hippocampus, and amygdala) (Broedel et al., 2003). These results show that, in particular, those areas in which D3 activity is very low or undetectable, such as the medulla, cerebellum, and midbrain (Pinna et al., 2002), are not well protected against hyperthyroidism. However, the hypothalamus, where D3 activity is no lower than in cortical areas (Pinna et al., 2002), is a notable exception, as hypothalamic concentrations of T3 were elevated drastically after administration of T3 and high-dose T4.

Transient neonatal hyperthyroidism produces an altered hippocampal morphology with larger mossy fiber terminal fields in the hippocampal CA3 region (Lauder and Mugnaini, 1977; Lipp et al., 1988). These morphological changes are accompanied by an improvement of spatial memory in the radial maze, but there is also an impairment of two-way active avoidance learning in the shuttle box (Lipp et al., 1988; Crusio and Schwegler, 1991; Schwegler et al., 1991). Thus, thyroid hormones influence both cognitive (spatial learning, two-way avoidance learning), and emotional factors (two-way avoidance learning). However, the morphological substrates of emotionality altered by transient neonatal hyperthyroidism are less clear. Possible candidates are peptidergic neurons, which occur in high numbers in brain regions involved in the control of emotional behavior, and especially in the amygdala. In the rodent hippocampus, naturally occurring variations of mossy fiber distribution and alterations induced by transient neonatal hyperthyroidism both correlate with different aspects of cognitive behavior (Schwegler et al., 1981, 1991; Lipp et al., 1988; Crusio and Schwegler, 1991).

On the other hand, the results obtained in hyperthyroid rats raise the question as to what mechanisms underlie the numerous biochemical and psychological abnormalities observed in hyperthyroidism. In light of the previous results, one research group, for example, observed decreases in the number of β-adrenergic receptors and norepinephrine-stimulated cAMP formation in rat cerebral cortex after 9 days of treatment with 50 μg T_4/kg day^{-1} (Schmidt and Schultz, 1985). Other authors have found an increase in cortical β-adrenergic receptor density after 7 days of treatment with 250 μg T_4/kg (Mason et al., 1987). This and numerous other contradictory results of studies on the effects of hyperthyroidism on brain parameters may well be because of the fact that a dose of 50 μg T_4/kg may even decrease brain T3 levels (Broedel et al., 2003). On the other hand, even discrete forms of hyperthyroidism cause mild to moderate psychiatric symptoms, such as nervousness, anxiety, fatigue, weakness, and hyperactivity in a substantial number of patients (Braverman and Utiger, 2000; Whybrow and Bauer, 2000). The effects of hyperthyroidism may theoretically also be mediated by elevated levels of T3 in other subcellular structures, such as the mitochondria or synaptosomes, and/or by other iodothyronine metabolites such as 3,5-T2 (Goglia et al., 1999); or by "peripheral" influences, such as changes in heart rate, oxygen supply, glucose availability, etc.; or finally by effects of the underlying disease, for example immunological effects on specific brain parameters in Graves' disease (Broedel et al., 2003). It is particularly intriguing that those mental and cognitive functions such as cognitive performance, mood, and anxiety, which are most often affected in hyperthyroidism, are mainly regulated in brain regions in which even high doses of T4 failed to induce increases in T3 concentrations (cortical areas, the hippocampus and amygdala). In light of these results, it does not seem surprising any more that the adult vertebrate brain has long been considered to be unresponsive to thyroid hormones (Leonard and Köhrle, 2000). Also, the manifestations of hyperthyroidism include anxiety, nervousness and tremulousness, irritability, tachycardia, emotional lability, physical hyperactivity, weight loss, increased perspiration, insomnia, weak muscles, increase in metabolic rates and, in serious situations, seizures (Orgiazzi and Mornex, 1990; Sarkar and Ray, 1994). It is possible that the effects of hyperthyroidism on brain function are the indirect result of thyroid hormone action on peripheral systems.

Amiodarone-induced thyrotoxicosis (AIT) and the management is a difficult challenge (Bartalena et al., 1996). Amiodarone and Iodide overload may produce thyrotoxicosis (Chiovato et al., 1997, Table 11). Russo-Carbolante et al. (2005) found that propylthiouracil and thiamazole are thionamides used in the treatment of hyperthyroidism. These drugs are thyrostatic and are used in the treatment of hyperthyroidism to inhibit the iodine organification that is one of the main steps in the formation of thyroid hormones, T3 and T4. Propylthiouracil has an additional action that is the impairment of the T4 to T3 conversion in extrathyroid tissues (Russo-Carbolante et al., 2005). Beta blockers drugs, iodides, antithyroid drugs (methimazole [1-methyl-2-mercaptoimidazole (tapazole)] and PTU), radioactive iodine, surgery (subtotal thyroidectomy) were used in the treatment of hyperthyroidism (Koornstra et al., 1999; Reid and Wheeler, 2005). Also, McGavack et al. (1947) said that 6-*n*-propylthiouracil is a safe and effective drug for the management of all forms of hyperthyroidism. For control of thyrotoxicosis,

thiourea derivatives, carbimazole (CMZ) and PTU, were both used (Kriplani et al., 1994). Thus, the proper treatment of hyperthyroidism depends on recognition of the signs and symptoms of the disease and determination of the etiology.

On other words, hyperthyroidism may initially induce an acceleration of the maturation processes, including the migration and differentiation of cells, the extension of the dendritic processes and synaptogenesis (Mussa et al., 1990). The early hyperthyroidism altered thyroid states and reduced the rate of cell acquisition in the EGL, but appear to do so for different reasons (Lauder, 1977a,b): Hyperthyroidism shortens the average length of the cell cycle by decreasing the duration of the pre-DNA synthetic phase (G1), indicating that excess thyroxine may exert a direct effect on the EGL. Furthermore, hyperthyroidism (Nicholson and Altman, 1972a) caused some malformations as a following: (1) decrease in body, brain and cerebellar weight; (2) early termination of cell proliferation in the EGL accompanied by early disappearance of this layer; (3) early cell differentiation in the molecular and internal granular layers; and (4) terminal decrease in granule cells, basket cells and astrocytes. Lauder et al. (1974) reported that hyperthyroidism can: (1) cause the premature decline and disappearance of the EGL; (2) decrease cortical growth; (3) decrease the amount of cerebellar foliation in the rat or an early maximization of the ratio of cortical to subcortical area, leads to early cessation of the folication process; and (4) reduce a number of fissures, which are, however, of normal depth. In the hyperthyroid rat, cell division is initially increased in the EGL but then is prematurely terminated (Lauder, 1977a,b). An acceleration in the morphological development of Bergmann glia cells was also observed in the hyperthyroid animals (Clos et al., 1980). Moreover, excessive doses of thyroxine or triiodothyronine led to an early stimulation of cell acquisition, followed by a permanent deficit of cells in the cerebellum (Legrand et al., 1976). Generally, hyperthyroid animals appear to have a shorter life and, at advanced age, show a myelin deficiency (Pasquini and Adamo, 1994). This may be due to the damage produced by the oxidative stress generated by an excess of thyroid hormones (Pasquini and Adamo, 1994). Based on the above results, the dramatic and profound neurological abnormalities associated with hyperthyroidism during the development testify to the importance and effect of the thyroid hormones on the CNS development. In general, during the critical periods of the development, increase or decrease in the thyroid secretions may retard the neurogenesis and CNS growth.

6. Comparison between the hypo/hyperthyroidism in human

See Table 14 (Halpern et al., 1991; Madeira et al., 1991; Avramides et al., 1992; Donati et al., 1992; Perelman and

Table 14
Comparison between the hypo/hyperthyroidism in human

Compare face	Hyperthyroidism	Hypothyroidism
Definition	It results from excessive levels of thyroid hormones T4 and T3, a low TSH	It occurs when T4 and T3 levels fall below physiologically required levels and increased levels of TSH
Causes	Graves disease	Hypothyroidism can be primary, secondary, or due to tissue resistance to thyroid hormone:
	Toxic multinodular goiter	(1) *Primary causes*
	Toxic adenoma	Destructive lesions such as Hashimoto thyroiditis
	Iodide-induced hyperthyroidism	Idiopathic myxedema
	Subacute thyroiditis	Radioactive iodine therapy for hyperthyroidism
	Factitious (exogenous) thyroiditis	Subtotal thyroidectomy (e.g., surgery for Graves disease)
	Neonatal thyrotoxicosis (e.g., pregnant mother with Graves disease)	Neck irradiation for other diseases
	TSH-secreting pituitary tumor	Following acute thyroiditis (can be transient)
	Nontumorigenic pituitary-induced hyperthyroidism	Cystinosis
	Choriocarcinoma (uterine or testicular origin) or hydatidiform mole	Defects in enzymes that are necessary for thyroid hormone synthesis (congenital goiter)
	Struma ovarii	Endemic goiter (iodine deficiency)
	Hyperfunctioning thyroid carcinoma (usually metastatic)	Iodine excess (>6 mg/day)
		Drug-induced thyroid agenesis
		Thyroid dysgenesis or ectopy
		Maternal iodide
		Antithyroid drugs
		(2) *Secondary causes*
		Hypothalamic dysfunction due to neoplasm
		Eosinophilic granuloma or therapeutic irradiation
		Pituitary dysfunction due to neoplasm
		Pituitary surgery or irradiation
		Idiopathic hypopituitarism
		Sheehan syndrome (i.e., postpartum pituitary necrosis)
		Dopamine infusion
		Severe illness
		Heatstroke

Table 14 (*Continued*)

Compare face	Hyperthyroidism	Hypothyroidism
Symptoms	(1) Confusion (2) Seizures (3) Nervousness and tremor, emotional lability (4) Muscle weakness (5) Heat intolerance, increased cardiac output at rest and after exercise (6) Weight loss (with increased appetite) (7) Palpitations	(1) Weakness, fatigue, lethargy, and somnolence (2) Cold intolerance, decreased sweating (3) Dry, coarse skin (4) Headache (5) Swelling of the face and extremities (6) Impaired memory and cognition, poor concentration (7) Mild weight gain (with anorexia) (8) Coarseness of voice and impaired hearing (9) Paresthesias and arthralgias (10) Muscle cramps and constipation
Physical manifestion	(1) Hyperthyroidism manifests systemically, affecting primarily muscle function and the central nervous system	(1) In infants, this results in cretinism, which manifests as delayed physical and mental development. Affected infants have enlarged tongues, a coarse cry, thickened subcutaneous tissues, potbelly, umbilical hernia, hearing defects, and speech defects
	(2) It is associated with neuropsychiatric and neurologic syndromes and myopathy (e.g., chronic thyrotoxic myopathy, exophthalmic ophthalmoplegia/infiltrative ophthalmopathy/Graves ophthalmopathy), thyrotoxic periodic paralysis, and myasthenia gravis	(2) Other findings are slowness and masking or disinhibition of facial expression
	(3) Neuropsychiatric syndromes include the following: (a) Patients may manifest irritability, nervousness, tremulousness, apprehension, emotional lability, and agitation (b) Major depression, anxiety, hypomania or mania, schizophreniform disorder, and delirium also may occur. Milder deficits in memory, complex problem solving, and attention may be present (c) Psychosis (visual and auditory hallucinations) is infrequent	(3) Strabismus may be noted (4) Some develop thalamic posturing, with severe motor deficits and a characteristic posture (5) When the patient is laid on one side, the undermost limb extends and the uppermost limb flexes (6) Other signs include microcephaly; inability to sit, stand, or walk; prominent primitive facial reflexes (especially the visual suck reflex); blepharospasm; and a prominent glabellar reflex
	(d) The clinical picture is seldom clear. The onset of symptoms is insidious, and often patients are referred to psychiatrists before the diagnosis is made (e) This is especially true for older patients, in whom dementia or depression is suspected (f) The presence of such symptoms may be related to the premorbid personality, but no definitive studies exist to support this theory (g) One of the difficulties in establishing the contribution of a premorbid personality is the inability of precisely determining the onset of thyroid dysfunction (h) Psychiatric symptoms have no direct relationship to the severity of the hyperthyroidism; once thyroid hormone levels are back to normal, the symptoms may resolve over months (i) Neurologic syndromes include chorea, ballism, embolic stroke secondary to tachycardia-induced atrial fibrillation, status epilepticus, and coma (which may occur in thyrotoxic crises) (k) Chronic thyrotoxic myopathy is a common complication: (i) This myopathy is characterized by progressive weakness and wasting of skeletal musculature (ii) Goiter of the nodular type is often present (and sometimes exophthalmos) (iii) More than 50% of thyrotoxic patients have some degree of myopathy (iv) The myopathy is slowly progressive; the pelvic girdle and thigh muscles are affected preferentially (j) Exophthalmic ophthalmoplegia also is known as Graves ophthalmopathy and infiltrative ophthalmopathy (i) This refers to weakness of external ocular muscles and exophthalmos from Graves disease (ii) Strabismus and diplopia may be present, as well as pain and lid retraction (iii) The term infiltrative ophthalmopathy refers to ocular muscle histology that suggests an autoimmune process: prominent fibroblastic tissue, degenerated fibers, and infiltration of lymphocytes, mononuclear leukocytes, and lipocytes (l) Thyrotoxic periodic paralysis resembles familial periodic paralysis and manifests with attacks of mild to severe weakness, during which serum potassium levels are generally low (m) Myasthenia gravis may be associated with hyperthyroidism (i) Hyperthyroidism is seen in 5% of patients with myasthenia gravis (ii) Conversely, incidence of myasthenia gravis is 20–30 times higher in hyperthyroid patients than in the general population (iii) Weakness and muscle atrophy from hyperthyroid myopathy can coexist with other abnormalities secondary to myasthenia gravis	(7) Patients appear autistic (i.e., total disregard of surroundings and absence of purposeful activity) (8) Other signs include the following: (a) Hypotonia, Cerebellar signs manifesting with ataxia, tremor, and dysmetria (b) Polyneuropathy and Cranial nerve deficits (c) Entrapment neuropathy (e.g., carpal tunnel syndrome) (d) Slowing of voluntary movements and Myopathic weakness (e) Neuropsychiatric signs—dementia, apathy, mental dullness, irritability, sleepiness

Table 14 (*Continued*)

Compare face	Hyperthyroidism	Hypothyroidism
Clinical signs and symptoms during pregnancy (Fantz et al., 1999)	Fig. 8	Fig. 9

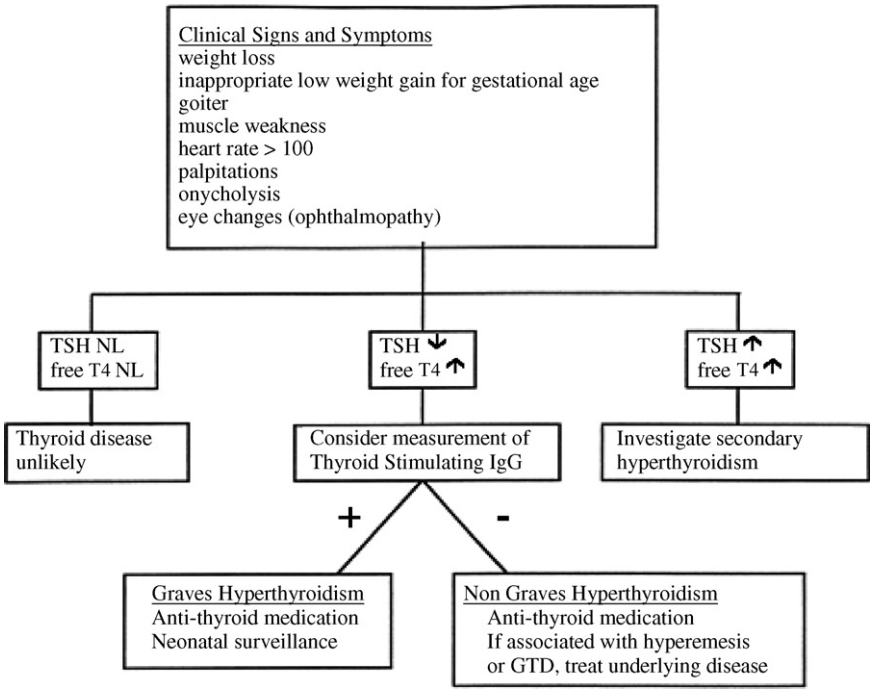

Fig. 8. Algorithm for the evaluation of hyperthyroidism during pregnancy. NL, within the reference interval; ↓, decreased; ↑, increased.

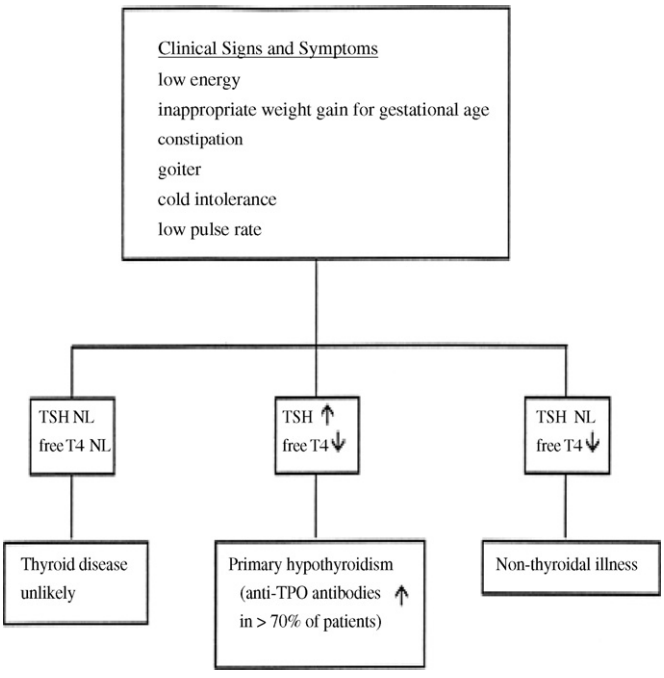

Fig. 9. Algorithm for the evaluation of hypothyroidism during pregnancy. NL, within the reference interval; ↑, increased; ↓, decreased.

Clemons, 1992; Boyages and Halpern, 1993; Quattrini et al., 1993; DeLong, 1996; Ozata et al., 1995, 1996; Ozkardes et al., 1996; Adams et al., 1997; Calzà et al., 1997; Lai et al., 1998; Jagannathan et al., 1998; Marta et al., 1998; Tamburini et al., 1998; Muthipeedika et al., 2005; Ozkan and Colak, 2005; Parker and Davidson, 2005; Sinclair et al., 2005; Losa et al., 2006).

7. Thyroid hormones and neurotransmitters interactions

7.1. Thyroid–cholinergic system interaction

Earlier work in adult progeny of Tx dams showed disturbances in brain choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) activities (Sinha et al., 1994). Alternatively, the more severe maternal hypothyroxinemia induced in the study of adult progeny T4 levels were depressed to only 10% of controls (Sinha et al., 1994), may be responsible. Evans et al. (1999) demonstrated that maternal thyroid status regulates the ontogeny of monoaminergic and, to a lesser extent, cholinergic neurotransmitter metabolic enzyme activities in rat brain. These changes are evident during fetal life

(from GD-16) when the neurotransmitters concerned have putative neurotropic roles, and may therefore have long-term repercussions for brain development (Evans et al., 1999). Compromise to monoaminergic metabolic enzymes during postnatal life, cholinergic ones may impinge upon neurotransmission and contribute to the behavioral dysfunction seen in young adult progeny of Tx dams (Sinha et al., 1994). These findings may be pertinent to humans, since maldevelopment of cholinergic and monoaminergic nerve pathways during the first half of gestation, when the mother determines the intrauterine TH environment, may contribute to the impaired cognitive and motor development reported in offspring of hypothyroxinemic women (Man et al., 1991). Brain acetylcholine levels were significantly elevated and the activity of acetylcholinesterase remained unchanged in rats made hypothyroid at 1 day of age (Singhal et al., 1975).

The cholinergic system in various brain regions is perhaps the most profoundly affected by neonatal thyroid deficiency (Patel et al., 1987; Gould and Butcher, 1989; Rami et al., 1989; Oh et al., 1991; Virgili et al., 1991). In fact, the activity of ChAT, an enzyme marker for cholinergic nerve terminals, is exquisitely sensitive to thyroid status. Additionally, hyperthyroidism has been shown to accelerate and hypothyroidism to delay the ontogenetic profiles of perikaryal sizes and dendritic arborization of the cholinergic neurons in the basal forebrain (Gould and Butcher, 1989). Patel et al. (1988) and Oh et al. (1991) further suggested that susceptibility of the developing cholinergic neurons to thyroid hormones might involve differential sensitivity to nerve growth factor. Interestingly, muscarinic cholinergic receptors in the developing brain are not subject to the influence of thyroid hormones (Patel et al., 1980a,b). The cholinergic pathways in the CNS are also known to participate in various cognitive and memory functions (Koliatsos et al., 1994; Everitt and Robbins, 1997). Specific lesions of these cholinergic fibers have been shown to interfere with learning and memory in spatial tasks (Kelsey and Landry, 1988; Okaichi et al., 1989; Nilsson et al., 1992; Berger-Sweeney et al., 1994; Torres et al., 1994; McAlonan et al., 1995; Stackman and Walsh, 1995). Because deficiencies in cognitive function are commonly found in hypothyroid human subjects and animal models, it is tempting to associate disruption of this neurotransmitter system in specific brain regions with impaired neurobehavioral development resultant from this hormonal imbalance. The effects of thyroid hormone imbalances on brain cholinergic neurons are regionally selective. Furthermore, brain region-specific alterations in AChE, ChAT and several myelin metabolic enzyme activities were described in adult experimental progeny (Pickard et al., 1997).

Cholinergic and aminergic neurotransmitter systems in rat brain are particularly susceptible to alterations in postnatal thyroid status, disruption occurring in neurotransmitter levels (Rastogi and Singhal, 1976a,b), metabolic enzyme activities (Kalaria and Prince, 1985; Virgili et al., 1991) and receptor numbers (Patel et al., 1980a,b; Smith et al., 1980). Similar findings have been reported in rat neural cell culture models (Garza et al., 1988).

7.2. Thyroid–serotoninergic (5-HT) system interaction

Recent studies in animals and humans have shown that thyroid hormones influence the activity of serotonin, as well as the functioning of its receptors (Tejani-Butt et al., 1993; Kulikov et al., 1999). Some evidence exists from neuroendocrine challenge studies in patients with thyroid dysfunction that the hypothyroid status is associated with reduced 5-HT responsiveness, which is reversible with thyroid replacement therapy (Cleare et al., 1995, 1996). Experimentally induced hypothyroid states result in an increase in 5-HT turnover in the brain stem (Henley and Koehnle, 1997). Also, thyroid hormone application may increase cortical serotonergic neurotransmission via two independent mechanisms: (1) a recent *in vivo* microdialysis study by Gur et al. (1999) indicated a loss of autoinhibitory serotoninergic receptor type 1A (5-HT_{1A}) receptor sensitivity mediated by T3. Bauer and Whybrow (2001) results revealed that thyroid hormone application may desensitize autoinhibitory 5-HT_{1A} receptors, and thus increase cortical and hippocampal serotonin release; and (2) by increasing cortical serotoninergic receptor type 2 (5-HT2) receptor sensitivity, creating a potentially independent way of increasing 5-HT transmission (Heal and Smith, 1998). A recent study in adult rats indicated synergistic effects of T3 and 5-HT_{1A} receptors on the expression of hippocampal brain-derived neurotrophic factor (BDNF) (Vaidya et al., 2001).

Evidence that serotonin, a neurotransmitter strongly involved in depressive states (Depressão, 1999), also has a pathophysiological role in thyroid diseases stems from several observations. Brain serotonin synthesis and turnover in rats decreased in hypothyroidism (Singal et al., 1975) and increased in hyperthyroidism (Atterwill, 1981). In human beings, serotonin plasmatic levels are positively correlated to T3 concentrations, being increased in hyperthyroidism, and with the decrease in the thyroid hormones due to antithyroid treatment, serotonin serum levels use to be reduced (Cleare et al., 1995). In animals with hypothyroidism, Atterwill (1981) found a decrease in the sensitivity of serotonin receptors and a compensatory increase in the density of $5HT_{1A}$ receptors, secondary to the reduction in the levels of synaptic serotonin (Tejani-Butt et al., 1993). In the investigation of the interaction between the thyroid function and the serotoninergic system, Cleare et al. (1995) reported a significantly decreased cortisol and prolactine response to the 5-HT d-fenfluramine agonist among patients with non-treated hypothyroidism, suggesting a decreased 5-HT central function in these cases. In a further investigation on the serotoninergic function in patients with hypothyroidism, Cleare et al. (1996) confirmed the previous findings and noticed that the serotoninergic function was normalized by reposition therapy with thyroid hormones. They have also concluded that the possibility that brain serotoninergic neurotransmission decreased in hypothyroidism and suggested that this reduction of 5-HT responsiveness is reverted with thyroid hormonal reposition. Thus, the previous publications supports the suggestion of Schwark and Keesey (1975) who said that thyroid hormone might exert an important regulatory influence on serotonin metabolism in the developing brain.

A probable reason why thyroid hormones interact with serotonin stems from the observation of the effect of these hormones on the serotoninergic auto-receptors. The administration of thyroid hormones on animals with induced hypothyroidism and on euthyroid animals has caused an increase in the cortical serotonin and a desensitivization of the $5HT_{1A}$ inhibitory self-receptors in the raphe (Heal and Smith, 1998). This functional decrease of self-receptors results in an increase in the cortical and hyppocampal 5-HT release (Heal and Smith, 1998). These findings were confirmed *in vivo* study (Gur et al., 1999), with euthyroid rats, which reported a significant decrease in the self-inhibitory sensitivity of the $5HT_{1A}$ receptor induced by administration of T3. These results were confirmed by Altshuler et al. (2001) who reported that the use of T3 can reduce the activity of the $5HT_{1A}$ self-inhibitory receptors and, then, increase the cortical release of 5-HT. Other source of evidence for the interaction of serotonin with thyroid alterations originates from studies with enzymes that metabolize the thyroid hormones (Bahls and de Carvalho, 2004). As seen before, intrabrain T3 is mainly the result of local production through deiodination of T4 by type II deiodinase enzyme and D2 enzymatic activity is increased in hypothyroidism and decreased in hyperthyroidism and type III deiodinase, contrastingly to D2, has its activity increased in hyperthyroidism and decreased in hypothyroidism (Kirkegaard and Faber, 1998). D2 activity increases the production of T3 in the brain and hypophysis, and consequently also the local production of serotonin. Kirkegaard and Faber (1998) supposed that D3 activity decreases the local concentration of T3 and, indirectly, brain serotonin. In both hypothyroidism and hyperthyroidism, the functioning of these thyroid-hormone-metabolizing enzymes can affect the brain levels of serotonin. On the other hand, it has been recorded (Nemeroff, 1989) that depression causes an inhibition of type II deiodinase enzyme leading to a decrease in the brain levels of T3 and consequently contributing to the decrease of serotonin in depressive pictures. Other way of analyzing the alterations of thyroid hormones found in cases of depression stems from the observation that TRH seems to undergo a constant inhibition due to the presence of serotonin (Morley, 1981). In fact, if there is a decrease in brain serotonin levels, it would produce an increase in brain TRH, which can, consequently, stimulate the secretion of TSH. However, comorbidity of depression and hyperthyroidism does not sustain the hypothesis of serotoninergic deficiency (Bahls and de Carvalho, 2004). Also, Savard et al. (1984) observed that neonatal hyperthyroidism induced very little modification of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA) and substance P concentrations in discrete nuclei of the rat brain. Further neuroendocrine studies are needed to assess subtypes of 5-HT receptors aiming to confirm and explain more specifically the pathophysiological condition of serotonin in thyroid alterations.

7.3. Thyroid–catecholaminergic (CA) system interactions

The catecholaminergic system was initially investigated because of the physiological association between sympathetic nervous system activity and thyroid hormones (Harrison, 1964). Thyroid hormones appear to play an important role in regulating central noradrenergic (NA) function, and it has been suggested that thyroid dysfunction may be linked with abnormalities in central NA neurotransmission (Whybrow and Prange, 1981). In the rat brain, the NA receptor systems are responsive to changes in HPT axis function; studies demonstrated that thyroidectomy results in region- and receptor-specific pre and post-synaptic NA system changes (Tejani-Butt et al., 2000). Thyroidectomy decreases ligand binding to β- and α_2-adrenergic receptors in the cortex and limbic regions of the rat brain. These changes can be reversed by administration of T4, suggesting a neuromodulatory link between thyroid hormones and central NA systems (Tejani-Butt and Yang, 1994). Further evidence for a thyroid–NA interaction stems from immunohistochemical mapping studies that indicate that T3 is concentrated in both nuclei and projection sites of central NA systems (Rozanov and Dratman, 1996). T3 is also delivered from the locus coeruleus to its NA targets via anterograde axonal transport. This suggests that T3 may function as a cotransmitter with norepinephrine in the adrenergic nervous system (Gordon et al., 1999). Taken together, Safaei and Timiras (1985) indicated that thyroid hormones, through their nuclear receptors, directly affect the activity of catecholaminergic enzymes in cultured, immature (undifferentiated) neurons.

As early as in 1969, Prange et al. proposed that T3 caused an increase in the sensitivity of the brain noradrenergic receptors. T3 acts, therefore, on the noradrenergic neurotransmission system and augments its effects probably increasing the activity of the post-synaptic β-adrenergic receptors (Whybrow and Prange, 1981). This action is similar to that provided by the celebrated antidepressive agents, what can explain the reason why T3 is efficient to maximize antidepressive therapies, even in euthyroid patients. In 1981, Whybrow and Prange hypothesized that thyroid hormones accelerate the recovery from depression, as they increase the function of the β-adrenergic receptors. In that same year, Morley identified that noradrenalin participates in the stimulation to the release of TRH and TSH. The decrease in the thyroid activity may result in the decrease in the activity of the β-adrenergic post-synaptic receptors, causing a functional decrease in the noradrenergic neurotransmission (Hendrick et al., 1998). Hyperthyroidism had no significant effect on the development of β-adrenergic receptors in the brain and led to a sustained increase in the forebrain in the activity of 5′-nucleotidase, an enzyme which is also associated with plasma membranes and has been proposed to play some role in neurotransmission (Smith et al., 1980).

Other widely accepted etiological hypothesis of depression is the deficiency of catecholamines, especially noradrenalin (Depressão, 1999), and there is some evidence associating this monoamine and the hypothalamus–pituitary–thyroid axis. Immunohystochemical experimental studies in animal brains showed that T3 has a high concentration in synaptosomes (Mason et al., 1993), especially those located in noradrenergic neurotransmission brain nuclei (Dratman et al., 1987). Afterwards, Rozanov and Dratman (1996) confirmed the previous findings and found increased T3 concentrations in the locus

coeruleus and in the lateral tegmental nucleus of rat brains. These studies suggest that T3 has some special function in these noradrenergic nuclei and some authors consider that T3 can exert a neuromodulating or neurotransmitting role in the central noradrenergic system (Altshuler et al., 2001). Such a distribution is performed anterogradely, reaching the noradrenergically innerved superior brain structures. Bahls and de Carvalho (2004) concluded highlighting that T3 functions as a cotransmitter of brain noradrenalin. In addition, the availability of noradrenalin is essential for the transformation of T4 into brain T3 (Levitt and Moore, 1978).

Adrenergic alterations occur in thyroid diseases (Bilezikian and Loeb, 1983). It was found an increased number of β-adrenergic receptors in the lymphocytes of animals and patients with hyperthyroidism, contrarily to what happens in hypothyroidism (Fregly et al., 1975; Bilezikian and Loeb, 1983). Henley and Koehnle (1997) mentioned that in rat brains there is a slight decrease in the cortical density of β, α_1 and α_2 receptors in hypothyroidism and an increase in hyperthyroidism. Linnoila et al. (1983) discussing the hypothesis of central hypothyroidism in endogenous depressive, which would be caused by the transformation of T4 into brain r T3, suggest that the deficiency of T3 in the brain can alter the noradrenergic neurotransmission, probably through an inversion between the adrenergic receptors, with the predominance of α-adrenergic over β-adrenergic ones. Other studies with animals have found a reduction in the β-adrenergic receptors in hypothyroidism, suggesting that TH can stimulate these receptors (Gross et al., 1980). The spectrum of classic symptoms of hyperthyroidism suggests that in addition to the effects of increased thyroid hormone affecting various organ systems, there is also a hyperadrenergic state (Levey and Klein, 1990).

Neonatal hyperthyroidism induced by daily administration of L-triiodothyronine results in an increased turnover of norepinephrine and 5-hydroxytryptamine (Singhal et al., 1975). These amine changes were accompanied by a marked rise in the spontaneous locomotor activity in hyperthyroid rats. In addition, neonatal hypothyroidism induced either by ^{131}I or by an antithyroid agent, methimazole, markedly decreased the concentrations of norepinephrine, dopamine and 5-hydroxytryptamine and the activity of their rate-limiting enzymes, tyrosine hydroxylase and tryptophan hydroxylase (Singhal et al., 1975). However, they reported that the levels of 5-hydroxyindoleacetic acid, the chief metabolite of 5-hydroxytryptamine were elevated in several regions of the brain. In addition, Puymirat (1985) found in neonatal hypothyroidism induced either by ^{131}I or by an antithyroid drug decreases the concentration of dopamine and noradrenaline at least in whole brain studies. On the opposite, experimental neonatal hyperthyroidism induced by daily administration of L-triiodothyronine increases the synthesis as well as the utilization of catecholamines. These changes are also associated with an alteration of catecholaminergic receptors (Puymirat, 1985). Rastogi and Singhal (1976a) said that elevated levels of dopamine metabolites (homovanillic acid and 3,4-dihydroxyphenylacetic acid) after exposing of developing rats to triiodothyronine may be due to an increased turnover of dopamine. In contrast, the steady-state levels of norepinephrine remained unaltered resulting in a significant increase in dopamine to norepinephrine ratio in several regions of the brain examined (Rastogi and Singhal, 1976a,b).

Thyroid hormones also potentiate the actions of catecholamines (the effects of which are prominent in the hyperthyroid state), and their effect on somatic and skeletal growth are in part mediated by stimulation of the synthesis and action of growth hormone and insulin-like growth factor (Ogilvy-Stuart, 2002). On the other hand, hyperthyroidism (caused by administering 15 μg T4/100 g bw for 25 days) accelerated the accumulation of catecholamines and serotonin (Jacoby et al., 1975). In addition, Mano et al. (1998) recorded that the changes in CA and CA metabolites are responsible in part for the central nervous system symptoms observed in hyperthyroidism and hypothyroidism. Sato et al. (1986) demonestrated that the CA appears to ameliorate thyroid hormone excess or deficiency. Also, changes in the level of catecholamines and related compounds in cerebral cortex have been demonstrated in thyroid disorders (Mano et al., 1998). Ito et al. (1977) estimated that the accumulation rates of 5-HT and dopamine (DA) in hyperthyroidism increased in pons-medulla and mesodiencephalon, respectively, while in hypothyroidism, 5-HT and DA content decreased in cerebral hemispheres and mesodiencephalon. In addition, only DA content decreased in cerebellum and pons-medulla (Ito et al., 1977). This report indicated that the influence of thyroid hormones on monoamines in the adult brain varies with the neurotransmitter and the brain area. Smith et al. (1980) reported the effect of thyroid status on β-adrenergic receptor binding and 5%-nucleotidase activity in the forebrain and the cerebellum of the rat during the first five postnatal weeks. They stated that hyperthyroidism led to a sustained increase in the forebrain in the activity of 5%-nucleotidase, although had no significant effect on the development of β-adrenergic receptors in the brain. Takeuchi et al. (1998) recorded that an increment of NA content was only accelerated in cerebral cortex. However, the content of DA was accelerated in hippocampus. These results suggest that thyroid hormones have an influence in most animal's species, especially during the so-called critical periods, characterized by periods of accelerated growth and differentiation. The catecholamine levels are decreased in the neurons of hypothyroid rats (Slotkin and Slepetis, 1984). The depression of brain activity observed in thyroid deficiency is also associated with a severe reduction in the number of β-adrenergic receptors (Smith et al., 1980). Generally, in the adult brain, hypothyroidism induced by surgical thyroidectomy decreases the rate of catecholamines synthesis, decreases the number of alpha noradrenergic receptors and has no effect on striatal dopaminergic receptors (Puymirat, 1985). In contrast, hyperthyroidism increases the rate of catecholamines synthesis and induced hypersensitivity of noradrenergic receptors. The binding of [^{3}H]spiroperidol to dopaminergic receptors in striatal membranes from 31-day-old, hypo- and hyperthyroid rats was significantly decreased, compared to euthyroids (Vaccari and Timiras, 1981). These alterations appeared to involve the density of dopaminergic receptors, and not their

affinity for the radioligand, the only exception being a hyperthyroidism-caused decrease in the dissociation constant.

Indeed, TH is localized in dopaminergic, noradrenergic and adrenergic fibers, because it is the first factor of the catecholamine biosynthesis pathway, although its concentration is low in noradrenergic and adrenergic fibers of the amygdale (Fallon et al., 1978; Asan, 1993, 1998). Nevertheless, increased levels of TH, dopamine, and chief metabolites of dopamine (homovanillic acid, 3,4-dihydroxyphenylacetic acid) have been already demonstrated in the striatum of young rats following neonatal hyperthyroidism, whereas norepinephrine levels were unaltered (Rastogi and Singhal, 1976a,b). It can be proposed that in the neonate thyroid hormones act on CA neuron activity mostly through a morphogenetic effect whereas in the adulthood they directly affect CA metabolism (Puymirat, 1985).

On the other hand, impairment of the dopaminergic system has been implicated in patients with restless legs syndrome (RLS) (Turjanski et al., 1999; Ruottinen et al., 2000; Eisensehr et al., 2001). Morover, Tan et al. (2004) observed that dopaminergic dysfunction is associated with thyroid disorders and RLS. In particular, dopaminergic dysfunction is present in a hypothyroid mouse model (Kincaid, 2001). Thyroid disorders are fairly common in clinical practice, and the etiologic link between dopaminergic dysfunction and RLS is of pathophysiologic relevance and a correction of underlying hyper- or hypothyroid state improved or resolved these symptoms (Tan et al., 2004). Generalized hyperactivity frequently observed in hyperthyroid state could be confused with RLS-like symptoms. Is there a theoretical link in the pathophysiology between RLS and thyroid disorders? Functional imaging and animal studies have provided evidence implicating dopaminergic system impairment in RLS (Turjanski et al., 1999; Ruottinen et al., 2000; Eisensehr et al., 2001). Levels of DA, NA and related compounds were lower in the cerebral cortex in hyperthyroid rats, whereas some of these neurotransmitters were elevated in hypothyroid rats (Mano et al., 1998). In a genetic model of hypothyroid mouse, a reduction in the number of nigral dopamine neurons and an associated repetitive movement disorder has been demonstrated (Kincaid, 2001). Despite these observations, there is still no clear evidence of a direct link between RLS and thyroid disorders. We can infer that the thyroid maldevelopment may cause the disturbance in the synthesis, release of CA. This in turn, may cause the CNS dysfunction in hypothyroidism or hyperthyroidism cases through the neurons impairment. Generally, the biogenic amines putatively disturbed in both affective and thyroid disorders (both hypo- and hyperthyroidism) and they may mediate some of aberrant behavior, emotion, mood and memory associations (Whybrow and Prange, 1981). These systems, specifically the norepinephrine and serotonin system, which have their origins in the brainstem and extend through the midbrain into the limbic system and cortex, modulate the activity of many of the brain regions related to emotion, mood and memory (Maes and Meltzer, 1995). Despite numerous studies, there is, so far, no clear conclusion on the effects of neonatal dysthyroidism on the development of each catecholaminergic group.

7.4. Thyroid and neuro-enzymes interactions

Several of the affected neurotransmitter systems are expressed in early fetal brain before the onset of electrical activity (Thomas et al., 1995; Zhou et al., 1995) when they are thought to have neurotropic activities (Leslie, 1993). Whether such TH-responsive neurotransmitter systems are also targets for maternal TH action during early fetal brain development has not been investigated. Total monoamine oxidase (MAO) activity was reduced at 16 and 19 GD, but normal at 21 GD. ChAT, on the other hand, activity exhibited a similar trend after effecting of maternal hypothyroxinemia on the pre- and postnatal ontogeny (Evans et al., 1995). These changes are consistent with the effects of TH insufficiency at later stages of brain development, as studied in *in vivo* and cell culture models. For example, total MAO activity is reduced by combined materno-fetal (Gripois and Fernandez, 1977a) or neonatal hypothyroidism (Gripois and Fernandez, 1977b). Furthermore, MAO activity is TH sensitive in neuroblastoma cell lines (Safaei and Timiras, 1985) and was reduced by maternal hypothyroxinemia. ChAT activity is also regulated by postnatal thyroid status *in vivo* (Kalaria and Prince, 1985) and induced by T3 in neuronal cultures (Garza et al., 1988). These results suggested that TH might regulate MAO and ChAT activities through common mechanisms both before and after the onset of fetal TH synthesis. In postnatal brain, TH is considered to act via nuclear TH receptors (Evans et al., 1999). TRs are present at detectable levels in rat fetal brain from 14 GD (Falcone et al., 1994), rising threefold by 16 GD (Pérez-Castillo et al., 1985). Thus, MAO activity is disrupted after 14 GD, coincident with the rise in TR number (Evans et al., 1999). Also, monoamine oxidase type A (MAO-A) activity might be either directly depressed during the goiterogenic treatment, or increased as the result of some kind of rebound effect after interruption of methimazole administration (Vaccari et al., 1983). Further work is required therefore to examine TH-mediated transcriptional regulation of neurotransmitter metabolic enzymes. Tyrosine hydroxylase (TyrH) and AChE are also regulated by postnatal thyroid status (Rastogi and Singhal, 1974) but were unaffected prenatally by maternal hypothyroxinemia. TyrH activity appears less TH-sensitive however, than ChAT in an *in vivo* model (Kalaria and Prince, 1985) or MAO-A in neuroblastoma cells (Safaei and Timiras, 1985), while AChE is less responsive than ChAT to T3 in neuronal cultures (Garza et al., 1988). Prenatal changes in brain AChE and TyrH activities may have occurred if more severe maternal hypothyroxinemia had been induced. The interpretation of findings from overtly hypothyroid rat dam models is however confounded by factors such as severe maternal metabolic compromise and placental maldevelopment (Bonet and Herrera, 1991). Thus, severe maternal hypothyroidism produces permanent deficits in body and brain weight, and brain protein concentration (Hendrich et al., 1997). Goya and Timiras (1991) found a decrease in the number of nuclear T3 receptors and increased tyrosine hydroxylase activity during the cell maturation after treatment with sodium butyrate (0.5 mM for 4 days) or nerve growth factor (NGF) (2 nM for 6 days).

Morover, maternal hypothyroxinemia was associated with reduced MAO activity in fetal whole brain at 16 and 19 days gestation (Evans et al., 1999) and a similar trend was observed for ChAT activity. In contrast, DOPA decarboxylase (DDC) activity was markedly elevated at GD-21 (Evans et al., 1999). Further study of these enzymes at GD-14 showed no differences between normal and experimental progeny suggesting they become TH sensitive after this age (Evans et al., 1999). TyrH and AChE activities were unaffected prenatally, but during postnatal development, the activities of TyrH, MAO, DDC and, to a lesser extent, AChE were increased in a brain region- and age-specific manner in experimental progeny (Evans et al., 1999). The prenatal disturbances noted in the previous study may have wide-ranging consequences since they occur when neurotransmitters have putative neurotropic roles in brain development. Furthermore, the chronic disturbances in enzyme activity observed during postnatal life may affect neurotransmission, thereby contributing to the behavioral dysfunction seen in adult progeny of hypothyroxinemic dams. The transferred TH accumulates within the fetal brain coincident with the expression of TH metabolic enzyme activities and T3 nuclear receptors (Porterfield and Hendrich, 1993; Pickard et al., 1997). It is possible therefore, that the critical period of TH-dependency of brain development begins prior to fetal thyroid function when an adequate maternal TH contribution is crucial. Indeed, the field studies in iodine-deficient endemias have shown that maternal serum T4 levels in hypothyroxinemic pregnancies correlate with subsequent motor and cognitive function in the children (Pharoah and Connolly, 1989). Furthermore, impaired intellectual and motor functions are also apparent in children born to hypothyroxinemic women in iodine-sufficient environments (Man et al., 1991). Previous studies utilizing Tx rat dam models have shown that adult progeny exhibit impaired motor performance, cognition and learning ability (Attree et al., 1992; Sinha et al., 1994), suggesting underlying neurotransmitter dysfunction. It thought that the compromise in adult brain function stems from the insult incurred during fetal life. In fact, the brain of fetal and postnatal Tx dam progeny exhibits a range of biochemical abnormalities, including changes in cellular protein and DNA concentrations, and ornithine decarboxylase activity (ODC) (Morreale de Escobar et al., 1985; Porterfield and Hendrich, 1993). During postnatal development in the rat, neurotransmitter systems and synaptogenesis constitute major targets for TH action (Porterfield and Hendrich, 1993).

Exposure of developing rats to triiodothyronine increased the endogenous levels of striatal tyrosine and tyrosine hydroxylase as well as the concentration of dopamine in hypothalamus, pons-medulla, mid-brain, striatum and hippocampus (Rastogi and Singhal, 1976a,b). Maternal hypothyroxinemia also disrupted the prenatal ontogeny of DDC, but only near term when the intrauterine TH environment is determined largely by the fetus. This effect may be a progressive consequence of the earlier TH deficit. Indeed, postnatal dysthyroidism has little effect on DDC activity (Virgili et al., 1991). DDC activity remained elevated postnatally in brain stem and cerebral cortex, indicative of long term or in the case of brain stem, permanent compromise to monoaminergic neurons. Chronic changes were also apparent for other enzyme activities, in particular TyrH in cerebral cortex and MAO in brainstem (Evans et al., 1999). Neonatal hypothyroidism induced either by ^{131}I or by an antithyroid drug decreases the activity of tyrosine hydroxylase at least in whole brain studies (Puymirat, 1985). Whereas thyroid deficiency in early life produced no appreciable change in whole brain monoamine oxidase activity, it was increased in mid-brain and decreased in the hypothalamus (Singhal et al., 1975). Hypothyroidism induced by PTU leads to a decrease while hyperthyroidism induced by thyroxine causes an increase in the enzymatic activity of MAO on the fetus brain (Gripois and Fernandez, 1977a,b). It appears that rat fetal MAO is under a strong thyroid control.

Interestingly, all the enzymes affected postnatally showed increased activity, and disturbances were confined to brain regions in which neurogenesis occurs during early gestation. However, no changes were seen in cerebellum, possibly because this region develops largely after the onset of fetal TH synthesis (Evans et al., 1999). These results confirmed and extended the previous observations in postnatal Tx dam progeny (Pickard et al., 1993), and strongly supported a prenatal origin for the postnatal disturbances. Neurotransmitters have putative neurotropic roles in early gestation (Leslie, 1993). It is therefore possible that neuronal differentiation is disturbed by maternal hypothyroxinemia thus leading to chronic brain maldevelopment and perhaps the observed postnatal effects. Alternatively, the early TH deficit may impact on other signals which regulate the development of monoaminergic neural pathways, such as polyamines (Slotkin and Bartolome, 1986). Indeed, ODC which regulates polyamine biosynthesis, is sensitive to maternal hypothyroxinemia in fetal and postnatal rat brain (Pickard et al., 1993). Treatment of rats with propylthiouracil for the first 30 days of postnatal life drastically retards the ontogenesis of d-amino acid oxidase (d-AAO) in the brain stem and cerebellum (Weimar and Neims, 1977). There is a marked terminal deficit of d-AAO in both the brain stem (−64%) and cerebellum (−67%) at 94 days (adults) despite the near euthyroid status at this age. On the other hand, hyperthyroidism significantly accelerates the development of d-AAO in both brain stem and cerebellum. Nonetheless, animals treated with thyroxine at the first month of life display a net deficit of cerebellar d-AAO content in adulthood (Weimar and Neims, 1977).

In general, biochemical dysfunction is generally confined to early developing brain regions and is associated with learning and motor deficits in adult progeny (Pickard et al., 1997). The catecholamine levels decreased in the neurons of hypothyroid rats (Slotkin and Slepetis, 1984). The depression of brain activity observed in thyroid deficiency is also associated with a severe reduction in the number of β-adrenergic receptors (Smith et al., 1980). In addition, Ito et al. (1977) indicated that the influence of thyroid hormones on monoamines in the adult brain varies with the neurotransmitter and the brain area considered. Hence, the alterations of neurotransmitters, a disturbance in the secretion and turnover, in the CNS might be

involved in the physiological and biochemical responses that occur during the thyroid dysfunction (hypothyroidism or hyperthyroidism). In the light of these observations, and consistent with the previous results, we can conclude that the deleterious effect of the thyroid hormones during the development may lead to CNS pathophysiology. The thyroidal status influences neurotransmitter systems, but the mechanisms of regulation are unknown. It appears that the intensity of neonatal dysthyroidism greatly varies, depending on the monoamine and the brain area studied. Thus, further studies need to be done to emphasize this concept.

8. Thyroid hormones, synaptogenesis and myelinogenesis interactions

Thyroid hormones are known to regulate neuronal outgrowth, myelination and synapse formation (Nunez, 1984; Legrand, 1986; Gould et al., 1991; Bernal and Nunez, 1995; Oppenheimer and Schwartz, 1997; Rodriguez-Pena, 1999; Durand and Raff, 2000; Koibuchi and Chin, 2000). Thyroid hormones also regulate development of certain cholinergic and dopaminergic neurotransmitter systems as mentioned previously (Puymirat et al., 1983; Oh et al., 1991). The cholinergic fibers projecting from the hippocampus to the basal forebrain, including the striatum, are particularly sensitive to thyroid hormone deficiency (Oh et al., 1991). These cholinergic fibers are important in memory and learning, and a well functioning cholinergic system is a prerequisite for performance on spatial learning tasks in rodents (Schwegler and Crusio, 1995). These brain regions (hippocampus, basal forebrain) have particularly high levels of thyroid hormone receptors during development and are sites where thyroid hormones regulate nerve growth factor (NGF) production (Charrasse et al., 1992; Figueiredo et al., 1993; Alvarez-Dolado et al., 1994). Thyroid hormones and NGF cooperate in the development of specific cholinergic systems in the central nervous system (Munoz et al., 1993), and thyroid hormones could regulate neurotransmitter development through their action on NGF production in these specific regions. Porterfield and Hendrich (1993) said that the neurotransmitter systems and synaptogenesis constitute major targets for TH action during postnatal development in the rat. On the other hand, hypothyroidism decreases ChAT quantities in brain regions innervated by these neurons (Oh et al., 1991) because thyroid hormones serve as positive regulatory factors for the ChAT gene (Quirin-Stricker et al., 1994). This drop in ChAT quantity is preceded by a drop in nerve growth factor receptor (NGFR) levels, suggesting that thyroid hormone actions could be mediated by its action on NGFR production (Oh et al., 1991). The development of both dopaminergic and cholinergic systems is delayed in hypothyroidism (Vaccari et al., 1990). In addition, T_3 regulates expression of the neuron-specific gene for synapsin I, an important protein regulating neurotransmitter release and synaptic plasticity (Di Liegro et al., 1995). Furthermore, hyperthyroidism may change the rate of synaptogenesis mainly as a consequence of the stimulation of axonal and dendritic growth rather than by affecting synaptogenic events directly (Lauder, 1978). In addition, Giguère et al. (1992) suggested that the synaptosomes could be another site of action of thyroid hormone where T3 could stimulate the development of specialized nervous structures or modulate the activity of various neurotransmitters during the development of chick embryo cerebral cortex. Hyperthyroidism, induced in rat pups by the daily intraperitoneal administration of 1 μg/g body weight triiodothyronine, facilitated the development of ChAT fiber plexuses in brain regions innervated by basal forebrain cholinergic neurons, leading to an earlier and increased expression of cholinergic markers in those fibers in the cortex, hippocampus and amygdale (Oh et al., 1991). On the other hand, thyroid hormones regulate gliogenesis and myelinogenesis (Balázs and Richter, 1973). Neonatal hyperthyroidism accelerates while hypothyroidism delays the deposition of myelin (Marta et al., 1998). Additionally in hypothyroid animals, the lipid composition of myelin is markedly reduced, and myelin structure of the myelin is altered (Rosman and Malone, 1977). Hypothyroidism causes a reduction of major myelin proteins, proteolipid protein, myelin basic protein and myelin associated glycoprotein, although the mechanism of this reduction for each protein is probably different (Ibarrola and Rodriguez-Pena, 1997). In hypothyroid cerebellum, myelination is reduced throughout the brain, due, in part, to delayed oligodendrocyte differentiation (Johe et al., 1996; Billon et al., 2001).

On other instance, hyperthyroidism, induced in rat pups by the daily intraperitoneal administration of 1 μg/g body weight triiodothyronine, facilitated the development of ChAT fiber plexuses in brain regions innervated by basal forebrain cholinergic neurons, leading to an earlier and increased expression of cholinergic markers in those fibers in the cortex, hippocampus and amygdale (Oh et al., 1991). Furthermore, they found that the hypothyroid treatment also reduced the quantity of ChAT puncta present during postnatal weeks 2 and 3, and, from week 4 and continuing through week 6, the number of ChAT-positive terminals in the telencephalic regions examined was actually less than the amount extant during the former developmental epoch. The effects of thyroid hormone on cholinergic projection neurons in the rat brain appeared relatively selective for cells in the basal nuclear complex because neither hypothyroid nor hyperthyroid treatment produced changes in the cell body areas of the phenotypically similar CAT-positive neurons of the pontomesencephalotegmental complex (Gould and Butcher, 1989). Thus, the thyroid dysfunction (hypo- or hyperthyroidism) may affect the rate of synaptogenesis and myelinogenesis.

9. Thyroid hormones and γ-aminobutyric acid (GABA) system interactions (Fig. 10)

THs have critical roles in brain development and normal brain function in vertebrates (Bernal, 2002). Since it was first determined that congenital hypothyroidism disrupts normal brain development (resulting in mental retardation, known as cretinism), there has been ongoing research on the role of THs that play in brain development (Ford and Cramer, 1977; Patel et al., 1980a,b). In particular, it appears that the GABA system is

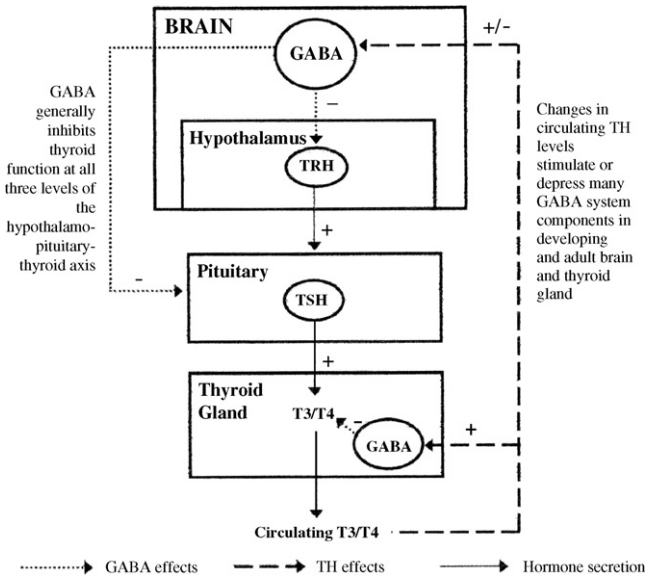

Fig. 10. Schematic representation of the possible interactions between the thyroid and GABA systems in vertebrates. GABA, γ-aminobutyric acid; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine. The + and − symbols indicate stimulation and inhibition, respectively (Wiens and Trudeau, 2006).

sensitive to THs. Underscoring the possible significance of the experimental evidence that THs regulate brain function by modulating GABA function and there is clinical evidence to suggest that some human nervous disorders involving alterations in GABAergic neurotransmission, such as anxiety and seizure susceptibility (Wiens and Trudeau, 2006). Recent evidence shows that GABA has critical roles in early neuronal development, even before synapses are formed (Represa and Ben-Ari, 2005). This suggests that neural impairment that results from disruptions in normal TH function during development could be due, at least partially, to TH effects on GABA function. The possibility that TH affects the GABAergic system was first recognized in the late 1960s (Ramirez de Guglielmone and Gomez, 1966). On the other hand, alternative animal models could be particularly useful in examining the TH–GABA connection given the fundamental role of TH in the control of amphibian central nervous system development and metamorphosis (Denver, 1998) as well as in profound seasonal variations in metabolism and reproduction in fish (Trudeau, 1997), birds (Yoshimura, 2006) and mammals (Pompolo et al., 2003; Yoshimura, 2006). *In vitro* study using fetal rat brain, cell cultures that mimic normal *in vivo* brain development, T3 application accelerated the developmental increase in glutamic acid decarboxylase (GAD; the key enzyme responsible for conversion of glutamic acid to GABA) activity (Honegger and Lenoir, 1980). As *in vivo* (e.g., Balázs et al., 1968), GAD activity *in vitro* increased with development, peaking at day 33 in culture. The addition of T3 resulted in GAD activity peaking at a similar level to control cultures, but at day 20 instead of day 33 (Honegger and Lenoir, 1980). In cultured fetal cerebral cortex neurons, T3 application accelerated the developmental increase in GAD activity (Aizenman and deVellis, 1987). T3 treatment also resulted in a higher specific activity of GAD at the end of the exposure period, 6 days in culture, but this effect was dependent on the presence of insulin in the culture medium (Aizenman and deVellis, 1987). Estradiol and hydrocortisone were tested without effect, suggesting that this action to increase GAD-specific activity is specific to TH (Aizenman and deVellis, 1987). Supporting these two *in vitro* studies, TH replacement to hypothyroid neonatal rats by subcutaneous T4 injections rescued GAD activity to control levels compared to the depression in GAD activity measured in hypothyroid animals 10 days after birth (Patel et al., 1988).

Thyroidal status influences the development of inhibitory cortical GABAergic circuits (Berbel et al., 1996). In hypothyroid rats from postnatal days 80–95, there was reduced parvalbumin immunostaining in the neocortex in comparison to controls (Wiens and Trudeau, 2006) and parvalbumin is a calcium-binding protein that is associated with a subpopulation of inhibitory GABAergic neurons and therefore is used to identify these neurons. Also, thyroid hormone receptor α (TRα) knockout mice show a major reduction in parvalbumin positive GABAergic terminals that are also immunoreactive for the GABA transporter1 (GAT-1), on pyramidal cells in the hippocampus in comparison to wild-type mice (Guadaño-Ferraz et al., 2003). It was concluded that this was likely due to a reduction in axonal arborizations of basket and chandelier cells rather than a reduction in cell number, because the total number of parvalbumin-positive cells was similar in knockout and wild-type mice (Wiens and Trudeau, 2006). This impairment of GABAergic circuit formation was correlated with changes in behavior that reflected hippocampal abnormalities, specifically reduced exploratory behavior in open field tests, and increased freezing response in contextual fear conditioning tests. Wiens and Trudeau (2006) discounted the possibility that the slightly hypothyroid state of TRα knockout mice caused the brain structure changes, as opposed to the absence of TRα, since brain T4 levels were not different, and T3 levels were only slightly higher than wild-type levels.

Neonatal hypothyroidism induced by various methods results in decreased GAD activity in various brain regions of rats in several studies (Garcia Argiz et al., 1967; Patel et al., 1988; Virgili et al., 1991) while resulting in increased GAD activity in one study (Kalaria and Prince, 1985). Virgili et al. (1991) found that hypothyroidism induced by methimazole injection on postnatal days 1–27 resulted in lower GAD activity measured on days 14 and 28 in frontal cortex, prefrontal cortex and visual cortex compared to controls, but no differences in hippocampus, striatum, cerebellum or superior colliculus during the injection period. Patel et al. (1988) showed that 10-day-old rats made hypothyroid by PTU administration to mothers 2 days before they gave birth, had lower basal forebrain GAD activity than controls. Balázs et al. (1968) elicited that rats rendered hypothyroid on the day of birth by administration of ^{131}I had 15% lower GAD activity in cerebral cortex grey matter compared to controls from days 17 to 32 after birth, a period in which GAD activity was increasing. GAD activities in both groups were similar after day 32 and continued to increase up to day 46. Garcia Argiz et al. (1967) studied the effects of ^{131}I-induced hypothyroidism on the developmental rise in GAD

activity in cerebellum and cerebral cortex in neonatal rats. Similar to the results of Balázs et al. (1968), the developmental rise in GAD activity was depressed in hypothyroid rats in comparison to controls after postnatal day 20. For cerebellum, GAD activity was approximately 25% lower only from day 20 until day 30, whereas for cerebral cortex, GAD activity was lower by 20–53% from day 20 until the end of the study, at day 50 (Garcia Argiz et al., 1967). Kalaria and Prince (1985) induced hypothyroidism in newborn rats by feeding PTU to mothers 2–3 days after birth until weaning at 4–5 weeks, then feeding the young rats PTU in food. On adult rat brain, hypothyroidism was induced by administration of PTU in food for 10–12 weeks (Kalaria and Prince, 1986). Visual cortex GAD activity was slightly higher in hypothyroid rats in comparison to controls and there was no difference in the corpus striatum (Kalaria and Prince, 1986).

Together with the work on hypothyroidism in neonatal rats, it seems possible that TH levels regulate GAD activity, with decreased TH levels resulting in lower GAD activity or slower development of GAD activity, and higher TH levels resulting in higher GAD activity or accelerated development of GAD activity (Wiens and Trudeau, 2006). However, in two studies, that measured neonatal brain GAD activity in response to *in vivo* TH administration to euthyroid animals (i.e., experimentally induced hyperthyroidism), there was no effect of excess TH on GAD activity (Patel et al., 1988; Virgili et al., 1991). This suggests that whereas a minimum amount of TH is required for normal GAD development in brain, excess levels will not affect development of GAD activity (Wiens and Trudeau, 2006).

THs also affect activities of other enzymes involved in the GABA metabolism pathway. The GABA-transaminase (GABA-T) and succinate semialdehyde dehydrogenase (SSDH) sequentially convert GABA to succinate and GABA-T is specific to the pathway and thus could be used as an indicator of changes in GABA metabolism (Wiens and Trudeau, 2006). In addition to measuring GAD activity in thyroidectomized neonatal rats as reported above, Garcia Argiz et al. (1967) also measured GABA-T and SSDH activities over 50 days after birth. Both enzymes showed increases in activity over that developmental period in both hypothyroid and control rats. In cerebral cortex, both enzymes had lower activities in hypothyroid animals compared with controls over the 50-day exposure. In cerebellum, GABA-T activity was lower over the entire 50-day exposure, but SSDH activity was only lower from days 15 to 30, having reached control levels by day 40 (Garcia Argiz et al., 1967). In a subsequent study, T3 replacement to hypothyroid rats restored GABA-T and SSDH activities back to control levels, when administered early enough (day 10) (Krawiec et al., 1969). Bovine growth hormone administration was able to rescue enzyme activities to control levels equally to T3 replacement, suggesting that effects of early hypothyroidism on brain development may not be due to direct effects of T3 but due to some indirect mechanism (Krawiec et al., 1969). Histochemical studies in cerebral cortex of hypothyroid rats also show that decreased TH levels result in transient decreases in GABA-T and SSDH activities in most cells (Pesetsky and Burkart, 1977). Therefore, in developing brain, hypothyroidism appears to result in lower activity of enzymes that synthesize GABA as well as degrade it, and TH replacement rescues enzyme activities to control levels.

GABA and glutamate levels have also been measured as indicators of *in vivo* changes in the GABAergic system in response to changes in thyroidal status in neonatal rats (Messer et al., 1989) and adult rats (Upadhyaya and Agrawal, 1993; Chapa et al., 1995). Neonatal rats rendered hypothyroid by ^{131}I injection within 2 h of birth had reduced whole brain glutamate and GABA concentrations compared with controls from days 16 to 30 after birth; after this point, they had control, adult concentrations (Ramirez de Guglielmone and Gomez, 1966). Thus, neonatal hypothyroidism results in overall decreased GABAergic function in developing rat brain. It is tempting to infer that the effects of hypothyroidism to decrease enzyme activities and neurotransmitter levels indicate a positive correlation between TH levels and GABAergic function (Wiens and Trudeau, 2006). However, in studies in which mice were made mildly hyperthyroid by T4 supplementation of the mother's food, glutamate and GABA levels were either slightly reduced or not affected at 2–4 weeks of age (Messer et al., 1989). Therefore, there is not a consistent positve correlation between circulating TH levels and GABA levels in developing brain. In adult rats, thyroidectomy followed by ^{131}I injection resulted in higher whole brain glutamate and GABA levels (Chapa et al., 1995), the opposite of what was observed in neonatal rats in response to ^{131}I injection (Ramirez de Guglielmone and Gomez, 1966). In another study on adult rats, hypothyroidism induced by intraperitoneal carbimazole injection resulted in higher GABA levels in cortex and hypothalamus and lower glutamate levels in the cortex and thalamus (Upadhyaya and Agrawal, 1993). The increased GABA level is consistent with the increase in GAD activity in visual cortex of adult rats in response to hypothyroidism (Kalaria and Prince, 1986) suggesting that hypothyroidism has opposite effects in developing versus adult rat brain. The effects of hyperthyroidism on glutamate and GABA levels in adult brain are more difficult to interpret. In one study, hyperthyroidism induced by intraperitoneal T4 injection resulted in higher glutamate and lower GABA levels in hypothalamus and thalamus (Upadhyaya and Agrawal, 1993) but in another study, there was no effect on whole brain GABA or glutamate levels (Chatterjee et al., 1989). In control rats, there was a significant positive correlation between plasma T3 levels and GABA levels in the hypothalamus and thalamus (Upadhyaya and Agrawal, 1993). This discounts the possibility that the experimental trends observed for adult rats (that lower TH levels result in higher GABA levels and higher TH levels result in lower GABA levels are due to a simple negative correlation between circulating TH levels and GABAergic function (Wiens and Trudeau, 2006).

GABA is released from the neuron into the synapse by the process of depolarization-induced Ca^{2+}-dependent exocytosis. Using *in vitro* preparations of synaptosomes from adult rat cerebral cortex, low nanomolar concentrations of T3, but not T4 or rT3, increased depolarization-induced GABA release by a

direct, nongenomic mechanism (Hashimoto et al., 1991). This effect could be due to increased Ca^{2+} uptake which had been observed in a previous study as a direct extranuclear effect of T3 on synaptosomes (Mason et al., 1990). One mechanism of GABA inactivation is its removal from the synapse by neuronal or glial cell plasma membrane GABA transporters (Wiens and Trudeau, 2006). Homogenates of corpus striatum from young rats made hypothyroid by PTU treatment from birth to 6 weeks of age had slightly increased GABA uptake and increased GAD activity (Kalaria and Prince, 1985). These significant increases, however, were lost when the values were expressed per striatum rather than per unit mass of tissue, suggesting that the effects were due to increases in cell packing rather than to increased GABA uptake or GAD activity within each cell (Kalaria and Prince, 1985). *In vitro*, T3, T4, and rT3 (in order of decreasing potency) competitively inhibited uptake of GABA by cerebral cortex homogenates of adult male rats by a nongenomic mechanism (Mason et al., 1987). Relatively high concentrations (micromolar) were required to have an effect. Therefore, Mason et al. (1987) questioned the physiological relevance of this effect. The effects of *in vivo* hypothyroidism and hyperthyroidism on *in vitro* GABA uptake were also studied (Wiens and Trudeau, 2006). Homogenates from rats rendered hypothyroid by surgical thyroidectomy demonstrated greater GABA uptake than controls, whereas homogenates from hyperthyroid rats demonstrated no difference in GABA uptake (Mason et al., 1987). This effect of long-term hypothyroidismwas assumed to reflect a genomic action of TH that was reduced due to lower TH levels. Perhaps THs inhibit GABA transporter synthesis, thus lower TH levels resulted in an increased number of transporters in neuron membranes and therefore greater GABA uptake by brain homogenates (Mason et al., 1987). In contrast to these results, using a similar *in vitro* method, no difference in GABA uptake in cerebral cortex homogenates of adult hypothyroid rats which caused by PTU administration in food for ten to 12 weeks in comparison to controls (Kalaria and Prince, 1986).

Hyperthyroidism in adult male rats, induced by 7 days of subcutaneous injection of T3 *in vivo*, resulted in fewer GABAbinding sites in the cerebral cortex, determined by *in vitro* binding of muscimol (Sandrini et al., 1991). However, hypothyroidism in adult male and female rats, induced by PTU in food for 10–12 weeks, had the same effect as hyperthyroidism in the study of Sandrini et al. (1991), resulting in fewer GABA-binding sites in the visual cortex (Kalaria and Prince, 1986). Overall, THs have effects on production and metabolism of GABA, levels of GABA and glutamate in brain, release and reuptake of GABA by neurons, and function of GABA receptors (Wiens and Trudeau, 2006). It appears that THs have differential effects on the GABA system in developing versus adult brain. THs generally act to stimulate GABA function, or development of GABA function, in developing brain, and to inhibit GABA function in adult brain and there is also good evidence that GABA regulates the function of the thyroid system. GABA has direct effects on the hypothalamus to inhibit TRH release, as well as inhibiting TRH-stimulated TSH release from the pituitary and TSH-stimulated TH release from the thyroid gland (Wiens and Trudeau, 2006). Despite a few conflicting reports it is likely that TH–GABA interactions are physiologically relevant, especially given the correlations between dysthyroidism and human neurological disorders with an underlying GABAergic component (Wiens and Trudeau, 2006). The effects of THs on the GABAergic systems in non-rodent and non-mammalian model organisms have yet to be investigated. On other word, Upadhyaya and Agrawal (1993) suggested that L-thyroxine and carbimazole administration cause marked alteration in biogenic amines and amino acids in rat brain, which may have an important role in the functioning of thyroid gland. In fact, Patel et al. (1987) indicateed that the effect of thyroid hormone on neural maturation is cell-type specific and the glutamatergic neurons are not the main targets of thyroid hormone action. Thus, pertaining to the previous studies, the current review suggests that, some nervous disorders involving GABAergic systems may relate to thyroid dysfunction (i.e., hyperthyroidism or hypothyroidism). It is generally, believed that GABA regulates the function of the thyroid system. GABA has direct effects on the hypothalamus to inhibit TRH release, as well as inhibiting TRH-stimulated TSH release from the pituitary and TSH-stimulated TH release from the thyroid gland. In fact, it was postulated that changes in thyroid axis function (see Fig. 10) may play a role in regulation of the immune response (Cremaschi et al., 2000).

Overall, the ontogenies of numerous CNS neurotransmitter systems that include catecholamines, acetylcholine, GABA and glutamate have been shown to be affected by neonatal thyroid deficiency (Schwark and Keesey, 1976; Patel et al., 1980a,b, 1987; Nagel-Hiemke et al., 1981; Vaccari and Timiras, 1981; Slotkin and Slepetis, 1984; Puymirat, 1985; Kalaria and Prince, 1986; Rami et al., 1989; Wiens and Trudeau, 2006). Alterations in CNS thyroid hormone levels have a major effect on the serotonergic, adrenergic and GABAergic systems (Brown et al., 2005).

10. Thyroid hormones and glucose 6-phosphate dehydrogenase (G6PD) interaction

Thyroid hormones regulate a variety of biochemical reactions in virtually all tissues. These hormones are known as important factors in gene regulation in tissues such as brain, liver, muscles and adipose tissue (Viguerie and Langin, 2003). They are also involved in the control of resting metabolism in rat (Moreno et al., 1997). Hypothyroidism in developing rat impairs synaptic transmission and has devastating effects on neurological functions that are permanent (Gilbert and Paczkowski, 2003). In brain, thyroid hormones affect the activities of enzymes such as malate dehydrogenase and hexokinase (Greengard, 1975). In this organ, pentose phosphate pathway shares an important portion of multiple pathways of glucose metabolism (Orosz et al., 2003). The activity of G6PD, the first enzyme of pentose phosphate pathway, has been affected by epinephrine in human hepatocytes (Haghighi et al., 1998) and by adrenal and sex hormones in rat liver (Haghighi et al., 1992).

In normal rats, the marked variations in G6PD activities of various brain regions might be attributed to the different

cellular structures of the regions. The cerebral cortex of the brain is accumulated with cell bodies of the neurons but midbrain consists mainly the neuron axons (Kandel et al., 2000). Since the cell bodies are the central locations of enzymes (Greengard, 1975), it seems likely that G6PD activity being higher in the cortex and lower in the midbrain than other brain regions. G6PD activities in striatum, hypothalamus and cerebellum are consistent with this hypothesis. These observations are also in agreement with the histochemical studies of the midbrain region (Brodal, 1980) and the higher G6PD activity in the olfactory bulb than other brain areas (Ninfalr et al., 1887). Generally, in normal rats, midbrain had the minimum (70 mU/mg) and cerebral cortex the maximum (349 mU/mg) G6PD activity (Haghighi et al., 2005).

Other report has shown that thyroid hormones influence the activities of lipogenic enzymes such as malic enzyme and G6PD (Lambardi et al., 2000). The effect of T3 on malic enzyme has been exerted at the transcriptional levels, but it is unclear whether the effect on G6PD is also nuclear mediated. The alterations were observed in G6PD activities of different brain regions; therefore, it could be associated with the different thyroid hormone concentrations in these regions. T3-binding protein from rat brain cytosol has been characterized and depended on NADPH, $NADP^+$ and thioredoxin (Lennon, 1992). Moreover, Haghighi et al. (2005) induced the hypo- and hyperthyrodism by methimazol and liothyronine, respectively, and they reported that: (1) In hyperthyroidism, the G6PD activities increased in straitum (72%), cerebellum (16%) and midbrain (144%) but did not significantly change in hypothalamus. (2) In hypothyrodism, the G6PD activities also elevated in straitum and midbrain but to a lesser extent and decreased in hypothalamus (73%) and cerebellum (45%). (3) The mechanism by which G6PD activities increased in striatum or midbrain by both hypo- and hyperthyroidism is unclear. (4) They said neither hypo- nor hyperthyrodism affected cerebral cortex G6PD activity.

Furthermore, the significant decrease in G6PD activity of hypothalamus in methimazole-injected rats is resulted from low concentrations of thyroid hormones in this area (Granner, 1988). Hypothalamus is the site for feedback control of hypothalamus/hypophysis loop of thyroid gland and the synthesis of thyrotropin-releasing hormone occurs in this site. TRH synthesis is inhibited by thyroid hormones and the pathway is mediated by dopamin and norepirephrine which, in turn, their synthesis require NADPH and NADH (Lichtensteiger, 1979). G6PD activity, therefore, plays an important role in this regard. In addition, Bockmann and Winter (1997) have reported that the expression of a TSH receptor in the CNS indicates that TSH is not only a hormonal messenger for the thyroid gland but also can act directly in the brain. A result of such action may cause alterations in G6PD activity in the brain regions. Generally, the biochemical maturation of the brain is delayed in hypothyroidism (Çalikoğlu, 1999). This includes retarded conversion of glucose carbons into amino acids Ğ an index of neuronal process development (Dasgupta et al., 2007).

From the previous results, we can suggest that the changes in G6PD activities of the brain regions may occur via different thyroid hormones effect on the regions. The increased G6PD activities in some regions may lead to fat accumulation and subsequently cellular disorders. This could explain the physiological and behavior changes observed in the animals following hypo- or hyperthyrodism treatments. Further studies are required to clarify the mechanism by which thyroid hormones affect G6PD activity in different brain regions.

11. Thyroid hormones and adenosinergic system interactions

Adenosine is an endogenous purine associated with an important modulatory role in neuronal activity and neuroprotective actions in pathological conditions (Latini and Pedata, 2001). The neuroprotective actions of adenosine are attributed to the activation of presynaptic A1 receptors, which reduce neurotransmitter release, depressing the neuronal activity in the CNS (Brundege and Dunwiddie, 1997; Dunwiddie and Masino, 2001). Adenosine is involved in various physiological and pathological processes, both in the periphery and in the CNS (Palmer and Stiles, 1995). Thus, adenosine plays an important regulatory role in the functioning, differentiation and survival of developing neural cells (Heilbronn et al., 1995). Adenosine formation may result from the sequential hydrolysis of ATP by an extracellular chain of ectonucleotidases, including the enzymes ecto-ATPase (EC 3.6.1.15), ecto-ATP diphosphohydrolase (ecto-apyrase, CD39, EC 3.6.1.5) and ecto-50-nucleotidase (CD73, EC 3.1.3.5) (Dunwiddie et al., 1997; Zimmermann, 1996). Previous studies have demonstrated that the ATP, released as a neurotransmitter, is hydrolyzed to adenosine by the conjugated action of an ATP and a 50-nucleotidase in brain synaptosomes (Battasttini et al., 1991; Bonan et al., 1998). Thus, alterations in these enzymes may have an important influence on neurotransmitter functions in the CNS. Therefore, the adenosine generated as the final product of this enzymatic cascade may affect the synaptic excitability, as well as the local blood flow, since adenosine is a powerful vasodilator (Rongen et al., 1997). Changes due to developmental stage have been demonstrated in adenine nucleotides hydrolysis-related enzymes activity in the CNS (Bruno et al., 2002). Furthermore, the brain receptors for ATP (P2) and adenosine (A1 and A2) are also modified in function of rat age (Amadio et al., 2002). Moreover, recent data demonstrated that the activation of the A1-adenosine receptors potently impairs the brain formation, since agonists of the A1-receptor decreased the cortical and hippocampal white matter volume, reflecting axonal losses (Rivkees et al., 2001; Turner et al., 2002). Thus, the increase in adenosine levels may activate the A1-receptors and trigger a cascade of events leading to impaired neural growth during development.

Previous studies demonstrated that the thyroid hormones might modulate both nucleoside transporters and adenosine receptors of the A1 subtype in the CNS (Fideu et al., 1994). In addition to their well-established role in cellular metabolism, thyroid hormones have critical effects upon cellular differentiation, growth, sensibility and synthesis of neurotransmitters (Engstron et al., 1974) and *in vitro* modulation of ecto-

nucleotidase activities in brain synaptosomes (Matos et al., 2002). Disorders involving thyroid hormones are common and can be accompanied by severe symptoms. Additionally, there is some evidence to demonstrate that the thyroid hormones are involved in the modulation of the adenosinergic system in the CNS. T3 increases the transport capacity and the number of adenosine transporters in neural cells (Fideu and Miras-Portugal, 1992).

Alterations in structure, function and behavior as a consequence of thyroid dysfunction, have highlighted the importance of these hormones, especially in central nervous system development and in the maintenance of neuronal system function throughout life (Smith et al., 2002). The inhibition of ATP, ADP and AMP hydrolysis observed in 5-, 30- and 60-day-old rats after the hyperthyroidism induction, may prolong the effect of nucleotides at their respective receptors and/or modulate various processes in the central nervous system (Bruno et al., 2003). Since ATP is recognized as an excitatory neurotransmitter in the central nervous system (Di Iorio et al., 1998) and a number of pathologies are associated with increased excitatory neurotransmission, the inhibition in ATP hydrolysis, observed herein, may have critical consequences. Several authors have described the important role of the ATP diphosphohydrolase, which maintains the physiological concentrations of the ADP in the process of haemostasis and thrombus formation (Marcus et al., 1997; Soslau and Youngprapakorn, 1997). Thus, hyperthyroidism affects both soluble and ecto-nucleotidases in different biological fractions and ages, consequently interfering in the balance of extracellular nucleotides and affecting the concerted function of the distinct physiological systems throughout the development. The presence of a shift in the balance of inhibitory and excitatory modulation after T4 treatment may be important for the understanding of the effects observed in hyperthyroidism.

On the other hand, hypothyroidism induced by thyroidectomy alters the adenosine receptors of the A1 subtype and reduces the adenosine transport in rat brain synaptosomes (Fideu et al., 1994). Hypothyroidism also induces a decrease in the activity of adenosine-metabolizing enzymes in different brain fractions (Mazurkiewicz and Saggerson, 1989) and an increase in plasma adenosine levels (Salin-Pascual et al., 1997). The activation of the 50-nucleotidase activity observed in the brain of rats submitted to neonatal hypothyroidism may represent modifications in adenosine production and possibly in expression of A1-adenosine receptors, which are detected in the brain on gestational day 14. The expression of the excitatory receptor A2A is much more restricted in fetal rats than the expression of the inhibitory receptor A1 (Weaver, 1996). Since adenosine inhibits the neuronal excitability and the release of neurotransmitters via A1-receptors (Brundege and Dunwiddie, 1997), changes in the adenosine levels may disturb these processes. This consideration is critic during brain development and may explain some cognitive disturbances that are observed in congenital hypothyroidism.

In addition to the well-established role of hypothyroidism in neonatal brain development, the mechanisms that involve the effects of thyroid hormone deficiency in mature brain are not fully understood. The 50-nucleotidase activity in hippocampal and brain cortical synaptosomes from 60- and 420-day-old rats was increased after hypothyroidism induction (Bruno et al., 2005). The sensibility to inhibitory agents, such as adenosine, is increased in the hypothyroid status (Ohisalo and Stouffer, 1979). Previous studies have demonstrated that adenosine transport and adenosine kinase activity are decreased in synaptosomal preparations in brain regions such as hippocampus and cerebral cortex from adult hypothyroid rats (Fideu et al., 1994; Mazurkiewicz and Saggerson, 1989). These previous results, taken together with the work showing increased 50-nucleotidase activity reported by Bruno et al. (2005), may result in a substantial increase in the brain adenosine levels, in turn, disturbing the hippocampal and cortical neurotransmission in adult hypothyroidism. Since neuromodulation exerted by adenosine includes the inhibition of the release of excitatory neurotransmitters, such as glutamate, hypothyroidism-related memory impairment is frequently associated with decreased excitatory transmission, mainly with glutamatergic transmission at the NMDA receptors (Lee et al., 2003). Other recent study has shown the influence of thyroid hormones on the 50-nucleotidase activity in glioma cells (Wink et al., 2003). To these cells, the ecto-50-nucleotidase is important to the cellular proliferation and differentiation, and enhanced levels of extracellular adenosine, could also be an important proliferation signal (Wink et al., 2003). Furthermore, the ATP hydrolysis was significantly increased in hippocampal synaptosomes from 420-day-old rats submitted to hypothyroidism indicating that the thyroid hormones deficiency may be activating the hippocampal ecto-ATPase (NTPDase2) activity during this developmental stage (Bruno et al., 2005). Therefore, the thyroid function undergoes a decrease in hypothalamic stimulation with the ageing process (Leitolf et al., 2002). Moreover, the decreased thyroid function, as well as a potential increase in the adenosine levels and a lower availability of ATP as an excitatory neurotransmitter, could be contributing to the severity of hypothyroidism during ageing (Bruno et al., 2005).

On other words, hyperthyroidism inhibits the ATP, ADP and AMP hydrolysis in synaptosomes from hippocampus and cerebral cortex of rats during different phases of development (Bruno et al., 2003). Hyperthyroidism, for example, is associated with a decrease in the ATP diphosphohydrolase and 50-nucleotidase activities in synaptosomes of rat hippocampus and cerebral cortex (Bruno et al., 2003). The increased levels of the neurotransmitter ATP together with decreased adenosine levels in a synaptic fraction originated mainly from neuronal cells could explain the predominantly excitatory status found in hyperthyroidism (Bruno et al., 2005). However, the effects of thyroid disorders on the adenine nucleotide hydrolysis-related enzymes from other brain sources are still unknown. Hyperthyroidism affects the extracellular nucleotides balance and adenosine production, interfering in neurotransmitter release, development and others physiological processes in different systems (Bruno et al., 2003). Hyperthyroidism inhibited the ATP and ADP hydrolysis very similarly (29% and 28%, respectively) in hippocampal slices (Bruno

et al., 2005). A parallel behavior for ATP and ADP hydrolysis is a characteristic of the ATP diphosphohydrolase (NTPDase1) previously described in this same preparation (Bruno et al., 2002). In addition, specific inhibitors of ATPases and alkaline phosphatase were ineffective as inhibitors of ATP, ADP and AMP hydrolysis by hippocampal and cortical slices (Bruno et al., 2005). These results suggest an effect on the NTPDase1, however the expression of this enzyme was not altered in hippocampus of hyperthyroid rats. In contrast to results obtained in hippocampal slices, the ATP and ADP hydrolysis was not altered by hyperthyroidism in slices from rat cerebral cortex. Bruno et al. (2005) showed that ATP and ADP hydrolysis are also inhibited after hyperthyroidism induction in the synaptosomal fraction obtained from hippocampus and cerebral cortex (Bruno et al., 2003). Since the synaptosomal preparation is predominantly comprised of neuronal cells, the presence of glial cells in cortical slices may be hiding the effect of thyroid hormones on the neuronal ATP diphosphohydrolase activity, observed earlier in cortical synaptosomes. Since ATP is recognized as an important excitatory neurotransmitter in the CNS (Di Iorio et al., 1998), the inhibition in ATP hydrolysis observed in hippocampal slices from hyperthyroid rats can disturb a number of processes related to brain excitability.

Furthermore, the effects of ATP as a cell death mediator are more prominent in fully differentiated brain (Amadio et al., 2002). ATP can also stimulate astrocyte proliferation, contributing to the processes of reactive astrogliosis, a hypertrophic response that is associated with some neurodegenerative disorders (Burnstock and Williams, 2000). The inhibition of excitatory neurotransmission mediated by adenosine is associated with processes, such as neuroprotection, decrease of motor activity, sedation, anticonvulsant actions, regulation of sleep and modulation of anxiety (Dunwiddie and Masino, 2001). Bruno et al. (2005) results demonstrated that hyperthyroidism significantly inhibited the activity of 50-nucleotidase in hippocampal and cortical slices of adult rats. In addition, the expression of 50-nucleotidase was also inhibited in hippocampus of these rats. Generally, a possible decrease in the extracellular adenosine levels in brain could be related to hyperthyroid rats. In contrast, the thyroid hormones deficiency increased the adenine nucleotide hydrolysis in slices from hippocampus and cerebral cortex. In addition, this increase was reverted by the T4 replacement treatment. ATP and ADP hydrolysis increased by 33% and 34%, respectively, in cerebral cortex from hypothyroid rats, indicating the same parallel effect mentioned above. Furthermore, the increase of ATP and ADP hydrolysis in hippocampal slices, may be attributed to NTPDase1, since the expression of this enzyme was also increased in hippocampus of hypothyroid rats. Additionally, the activation of the activity and expression of the 50-nucleotidase by hypothyroidism and the potential increase of the neuromodulation mediated by adenosine may contribute to the genesis of some clinical characteristics elicited by changes in neurotransmission and previously described in hypothyroid brain (Shuaib et al., 1994). It was also demonstrated that hyperthyroidism inhibits the 50-nucleotidase activity in hippocampal and cortical synaptosomes from adult rats (Bruno et al., 2003), whilst hypothyroidism increases the 50-nucleotidase activity in these same preparations (Mazurkiewicz and Saggerson, 1989). Previous studies have described the ecto-50-nucleotidase in the neuron surface; however, the most common localization of this enzyme in the brain is in the glial cells (Kreutzberg et al., 1986). Moreover, the hypothyroidism effect on adenine nucleotide hydrolysis in hippocampus was greater than in cerebral cortex. This result can be attributed to the raised vulnerability of hippocampus to postnatal and adult hypothyroidism (Madeira et al., 1992). Hippocampus is crucially involved in mental processes, such as learning and memory, but it is extremely sensitive to toxic events, such as a massive glutamate release and to microenvironment signals including hormones (Calzà et al., 1997). Furthermore, hyperthyroidism is associated with an increase in the transport and metabolism of adenosine and a simultaneous decrease in membrane ecto-50-nucleotidase activity in heart, altering this important endogenous cardioprotective mechanism (Smolenski et al., 1995). Therefore, the hippocampal ecto-nucleotidases may also be more vulnerable to hormonal variations or to brain injury produced by these variations. Thus, hyperthyroidism affects the complete enzyme cascade responsible for the hydrolysis of ATP to adenosine, whereas hypothyroidism seems to directly interfere in adenosine production in the synaptosomal fraction. Although hyper- and hypothyroidism affect distinct biochemical events, both thyroid diseases are able to influence the adenosine production in brain synaptosomes (Bruno et al., 2005). From the previous studies, this review hypothesized that both excess and deficiency of thyroid hormone are capable of inducing changes in the enzymatic cascade responsible for the hydrolysis of ATP to adenosine and an imbalance in the CNS-adenosine system especially during the development, depending on the brain region studied. These effects are in agreement with the clinical manifestations ascribed to hyper- and hypothyroidism, and then, may help us to understand some of the features related to these disorders. In normal, the adenosinergic system plays a crucial role also for the survival and differentiation of neural cell.

In other instance, the synaptic transmission is regulated by neurotransmitters and is dependent on action potential (Gilbert, 2004). The action potential in turn is regulated by the synaptic plasma membrane Na^+, K^+-ATPase (Peng et al., 1997; Gilbert, 2004). In addition, synthesis of specific proteins important for signal transduction and release of neurotransmitters is regulated by thyroid hormones (Neveu and Arenas, 1996; Garcia and Strehler, 1999; Mussa et al., 2001; Vara et al., 2003; Gerges and Alkadhi, 2004). In earlier studies, the neonatal hypothyroidism significantly altered the kinetic properties of Na^+, K^+-ATPase originating from the synaptic membranes (Billimoria et al., 2006). Neonatal hypothyroidism results in an impairment in synaptic transmission, diminished metabolic and electrical activities (Arnold et al., 2003; Gilbert and Paczkowski, 2003; Sui and Gilbert, 2003; Gerges and Alkadhi, 2004), and impaired neuronal and oligodendrocyte functions (Mussa et al., 2001). In the synaptic membranes, this enzyme is important for maintaining the action potential (Peng et al., 1997); however, significant Na^+, K^+-ATPase activity is also present in the

microsomes (Peng et al., 1997). So, whether neonatal hypothyroidism also affects the kinetic properties of brain microsomal Na^+, K^+-ATPase. In hypothyroid rats, the neuronal density of the CA3 hippocampal region is reduced and this reduction reflect a consequence of the decrease in Na^+, K^+-ATPase activity. These results do not agree with Madeira et al. (1992) who described a decrease in pyramidal neurons of the CA1, but not the CA3 region in hypothyroid rats. They reported a reduction in the volume of the CA3 pyramidal cell layer without a change in the total number of pyramidal cells. In addition, the deficiency of thyroid hormones also produce a deficiency of Na^+,K^+-ATPase in the brain (Schmitt and McDonough, 1986), which could produces alterations in the excitatory pathways of the hippocampus because the uptake of glutamate into glial cells and neurons in the central nervous system shows a sodium-gradient dependence (Amato et al., 1994). Billimoria et al. (2006) reported that the neonatal hypothyroidism severely impaired the Na^+, K^+-ATPase activity in synaptic membrane. However, apparently the Mg^{2+-}ATPase activity was not affected.

Regulation of Na^+, K^+-ATPase is a complex process controlled by several factors. These include the subunit composition, stoichiometry of the subunits and interaction of the enzyme with membrane proteins (Blanco and Mercer, 1998; Lopina, 2001; Cornelius and Mahammoud, 2003). As it is well documented, the enzyme comprises α, β and γ subunits (Blanco and Mercer, 1998; Lopina, 2001; Cornelius and Mahammoud, 2003). The α is the catalytic subunit while β functions as the regulatory subunit (Blanco and Mercer, 1998; Lopina, 2001; Cornelius and Mahammoud, 2003). Four isoforms of α (α 1–4) and three isoforms of β (β 1–3) subunits have been reported (Blanco and Mercer, 1998). The γ subunit 'FIXIT' plays a crucial role in the anchoring of the enzyme in the membrane (Cornelius and Mahammoud, 2003). As cited in the literature, the α3 is the major subunits in the brain although presence of α1 and α2 in cell subtypes has been reported (Peng et al., 1997). Interestingly, α2 seems to be the major subunit in the neuronal cells (Blanco and Mercer, 1998). Likewise, β1 seems to be the major subunit in the CNS although β2 is also present in specific cell types (Blanco and Mercer, 1998). Subcellular localization for α and β subunit isoforms is not clear at this stage (Blanco and Mercer, 1998). The different isoforms of α and β subunits seem to be regulated differentially in the tissue specific manner by the thyroid hormones (Desai-Yajnik et al., 1995; Hensley et al., 1994; Ohara et al., 1993). Schmitt and McDonough (1998) reported that during postnatal development, T3 regulates the α^+ isoform of the enzyme between the 15th and 25th postnatal days but not in the adults. Nomura et al. (1990) reported that the number of ouabain binding sites decreased in the cerebral cortex and the cerebellum of hypothyroid rats and significantly increased in response to T3 treatment. Chaudhury et al. (1996) depicted that, in the developing rat brain, the α3 mRNA is expressed as a major component and that the expression is severely reduced in hypothyroidism and the treatment with 200 μg T3/100g bw stimulated expression of all isoforms of α subunits. Interestingly, in the skeletal muscles, thyroid hormones seem to regulate the α2 isoform (Azuma et al., 1993). Banerjee and Chaudhury (2001) had also reported thyroid hormone sensitivity of the isoforms of the Na^+, K^+-ATPase subunits in the glial cell. Moreover, the neonatal hypothyroidism results in an impairment of microsomal Na^+, K^+-ATPase activity in the rat brain, together with subtle alterations in the kinetic properties of the enzyme (Katyare et al., 2006). Hypothyroidism induced by PTU from day 1 postnatally significantly reduced the Na^+, K^+-ATPase activity in cerebellum (22–30 days) but not forebrain, whereas hyperthyroidism (T_4 treatment from day 1) had no effect (Atterwill et al., 1985). These results show that neonatally induced hypothyroidism leads to a selectively greater impairment of the ontogenesis of the activity of cerebellar α form of Na^+, K^+-ATPase. This may possibly reflect a retarded development of a selective cerebellar cell population containing predominantly the α form of the enzyme. In other instance, the bidirectional transcellular transport of iodide inside thyroid follicles brings into play several distinct membrane proteins endowed with a function of ion transporter, either active or passive or with a function of ion channel; at present, only one of these molecular species is identified, the Na^+/iodide symporter (Rousset, 2006). Based on the above observations, the thyroid dysfunction induced impairment in the function of Na^+, K^+-ATPase can disturb the cellular ionic homeostasis. This in turn could result in impaired nerve transmission and cognitive functions.

Furthermore, the synaptic membrane Ca^{2+}-ATPase is believed to function as a Ca^{2+} pump and thus regulates the intracellular free [Ca^{2+}]. The microsomal Ca^{2+}-ATPase, on the other hand, regulates intracellular free [Ca^{2+}] by sequestering the cation in an energy-dependent manner (Zylinska and Soszynski, 2000). Impaired Ca^{2+} metabolism has been noted in several disease conditions including glutamate-induced exitotoxicity (Missiaen et al., 2000; Ramonet et al., 2002). It has also been reported that thyroid hormones, particularly triiodothyronine, produced a prompt and extremely rapid influx of Ca^{2+} in thymocytes raising the intracellular Ca^{2+} concentration (Segal and Ingbar, 1989). It is not clear whether a similar situation would prevail in the brain cells; it is possible that neonatal deprivation of thyroid hormones could result in either lowering of the free intracellular [Ca^{2+}] by itself or in lowering the content of sequestered Ca^{2+}. Either of the factors could impair the process of signal transduction.

However, it is not clear at this stage if the synthesis of Ca^{2+}-ATPases, which are single polypetides (Lin and Way, 1982), is also regulated by thyroid hormones. The ATPase activity in general is regulated by several factors that include membrane milieu and availability of the substrate, ATP besides subunit composition (Patel et al., 1993; Peng et al., 1997; Katewa and Katyare, 2003). The thyroid hormones have been shown to regulate the lipid/phospholipid biosynthesis and thereby the membrane lipid/phospholipid composition (Bangur et al., 1994; Wrutniak-Cabello et al., 2001). Dependence of membrane ATPases on specific phospholipids classes is well recognized (Patel et al., 1993). Thus, the altered membrane lipid/phospholipid milieu could be a regulatory factor. Besides, the rate of ATP synthesis decreases significantly in the

hypothyroid state thereby creating a deficiency of ATP (Katyare et al., 1977; Wrutniak-Cabello et al., 2001). The Ca^{2+}-ATPase function in both the membranes can get further impaired due to decrease ATP synthesis in the hypothyroid brain (Katyare et al., 1977; Katyare and Rajan, 2005). In conclusion, these results suggest that hypothyroidism induced impairment in the function of Ca^{2+}-ATPase can disturb the cellular Ca^{2+} homeostasis. This in turn could result in impaired nerve transmission and cognitive functions. Taken together, Zamoner et al. (2006) also evidenced differential mechanisms of action for T3 and T4 targeting the cytoskeleton in cerebral cortex from 10-day-old rats, supporting that T3 and T4 can nongenomically alter distinct signal-transducting pathways. Furthermore, T3 and T4 have membrane-initiated actions modulating Ca^{2+} channels, suggesting the presence of multiple sites of hormonal regulation and supporting a role for TH as modulators of signal transduction pathways in the CNS.

It can be inferred from the above mentioned results that the impairment of Na^+, K^+-ATPase and Ca^{2+}-ATPase activities as a consequence of thyroid hormone alterations during critical stages of brain development could be one of the underlying biochemical mechanism and central nervous system (CNS) dysfunctions. This in turn could result in impaired nerve transmission and cognitive functions.

12. Thyroid hormones and pro/antioxidant defense systems interactions

Oxidative stress may be defined as the measure of steady-state level of reactive oxygen or oxygen radicals in a biological system (Konukoğlu et al., 1998). Reactive oxygen species (ROS) including partially reduced forms of oxygen, i.e., superoxide anion, hydrogen peroxide and hydroxyl radical, as well as organic counterparts such as lipid peroxides, are produced as natural consequences of the oxidative cell metabolism (Halliwell and Gutteridge, 1984; Riley, 1994). Also, brain tissues are rich in phospholipids, which can be attacked by the highly ROS for the initiation of lipid peroxidation (Garcia et al., 2005). The brain is particularly vulnerable to oxidative damage because of its high oxygen utilisation, its high content of oxidizable polyunsaturated fatty acids, and the presence of redox-active metals (Cu, Fe) (Valko et al., 2007). Oxidative stress increases with age and therefore, it can be considered as an important causative factor in several neurodegenerative diseases, typical for older individuals. Defence mechanisms against free radical-induced oxidative stress involve (Cadenas, 1997; Valko et al., 2007): (1) preventative mechanisms; (2) repair mechanisms; (3) physical defences; and (4) antioxidant defences. Enzymatic antioxidant defences include superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GSSGR), glutathione-*S*-transferase (GST) and catalase (CAT). Non-enzymatic antioxidants are represented by ascorbic acid (Vitamin C), α-tocopherol (Vitamin E), glutathione (GSH), carotenoids, flavonoids, and other antioxidants. Under normal conditions, there is a balance between both the activities and the intracellular levels of these antioxidants (Ahmed, 2002). This balance is essential for the survival of organisms and their health. Various pathways for the management of oxidative stress by GSH and other antioxidants are shown in Fig. 11. Thus, the various roles of enzymatic antioxidants and non-enzymatic in the protection against oxidative stress can be found in a numerous reviews and original papers (see Fig. 11) (Cameron and Pauling, 1976; Burton and Ingold, 1984; Halliwell and Gutteridge, 1984; Packer and Suzuki, 1993; Makropoulos et al., 1996; Nakamura et al., 1997; White et al., 1997; Carr and Frei, 1999; Mates et al., 1999; Ahmed, 2002; El-Agamey et al., 2004; Kojo, 2004; Sharoni et al., 2004; Smith et al., 2004; Landis and Tower, 2005; Miller et al., 2005; Schrauzer, 2006; Valko et al., 2007).

Moreover, Betteridge (2000) reported that the free radicals can be produced by several different biochemical processes within the body including: (1) The reduction of the molecular oxygen during aerobic respiration yielding superoxide and hydroxyl radicals; (2) By products of chemical reactions such as oxidation of catecholamine and activation of the arachidonic acid cascade product electrons, which can reduce molecular oxygen to superoxide; (3) Production of superoxide and hypochlorous acid (HOCl), a powerful oxidant, by activated phagocytes and (4) Nitric oxide production by vascular endothelium and other cells. Moreover, antioxidant enzymes counteract excessive formation and deleterious effects of reactive oxygen metabolites (Ahmed, 2002). For example,

(1) Superoxide dismutase (SOD) catalyzes the conversion of superoxide anion radical to H_2O_2.
(2) Catalase (CAT) reduces H_2O_2 to water:

$$2H_2O_2 \rightarrow 2H_2O + O_2$$

(3) Glutathione peroxidase (GPx) acts in conjunction with other enzymes to reduce H_2O_2 and to terminate lipid peroxidation. Changes in antioxidant activities may occur under conditions that alter the rates of formation of reactive oxygen radicals.
(4) The glutathione reductase (GSSGR) enzyme catalyses the reduction of glutathione in the presence of NADPH, which was oxidized to $NADP^+$:

$$NADPH + H^+ + GSSG \rightarrow NADP^+ + 2GSH$$

(GSH is the reduced glutathione form, while GSSG is the oxidized one).

Generally, a great number of physiological functions are controlled by redox-responsive signalling pathways (Dröge, 2002). These, for example involve: (1) redox regulated production of NO; (2) ROS production by phagocytic NAD(P)H oxidase (oxidative burst); (3) ROS production by NAD(P)H oxidases in nonphagocytic cells; (4) regulation of vascular tone and other regulatory functions of nitric radical ($NO^{\bullet}$); (5) ROS production as a sensor for changes of oxygen concentration; (6) redox regulation of cell adhesion; (7) redox regulation of immune responses; and (8) ROS-induced apoptosis and other mechanisms. On the other hand, the disturbance of the prooxidant/antioxidant balance resulting

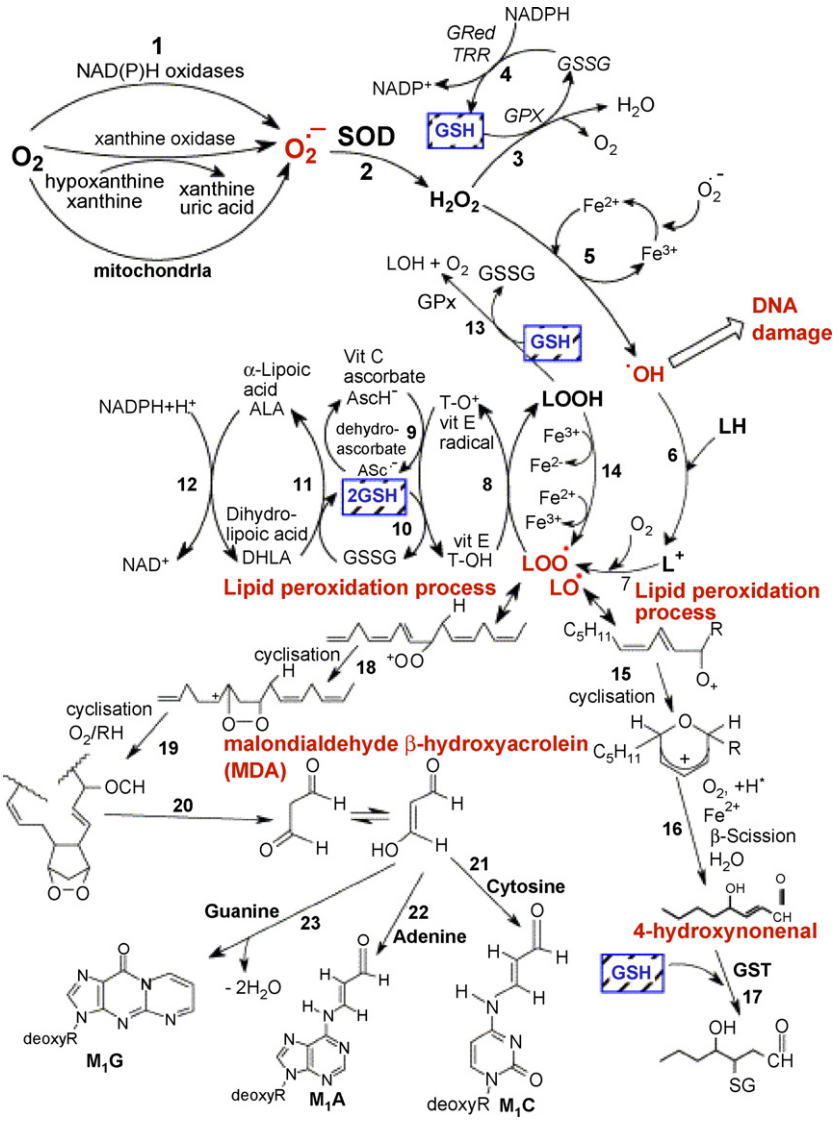

Fig. 11. Pathways of ROS formation, the lipid peroxidation process and the role of glutathione (GSH) and other antioxidants (Vitamin E, Vitamin C, lipoic acid) in the management of oxidative stress (equations are not balanced). Reaction 1: The superoxide anion radical is formed by the process of reduction of molecular oxygen mediated by NAD(P)H oxidases and xanthine oxidase or non-enzymatically by redox-reactive compounds such as the semi-ubiquinone compound of the mitochondrial electron transport chain. Reaction 2: Superoxide radical is dismutated by the superoxide dismutase (SOD) to hydrogen peroxide. Reaction 3: Hydrogen peroxide is most efficiently scavenged by the enzyme glutathione peroxidase (GPx) which requires GSH as the electron donor. Reaction 4: The oxidized glutathione (GSSG) is reduced back to GSH by the enzyme glutathione reductase (Gred) which uses NADPH as the electron donor. Reaction 5: Some transition metals (e.g., Fe^{2+}, Cu^{+} and others) can breakdown hydrogen peroxide to the reactive hydroxyl radical (Fenton reaction). Reaction 6: The hydroxyl radical can abstract an electron from polyunsaturated fatty acid (LH) to give rise to a carbon-centred lipid radical ($L^{\bullet}$). Reaction 7: The lipid radical ($L^{\bullet}$) can further interact with molecular oxygen to give a lipid peroxyl radical ($LOO^{\bullet}$). If the resulting lipid peroxyl radical $LOO^{\bullet}$ is not reduced by antioxidants, the lipid peroxidation process occurs (reactions 18–23 and 15–17). Reaction 8: The lipid peroxyl radical ($LOO^{\bullet}$) is reduced within the membrane by the reduced form of Vitamin E (T-OH) resulting in the formation of a lipid hydroperoxide and a radical of Vitamin E ($T\text{-}O^{\bullet}$). Reaction 9: The regeneration of Vitamin E by Vitamin C: the Vitamin E radical ($T\text{-}O^{\bullet}$) is reduced back to Vitamin E (T-OH) by ascorbic acid (the physiological form of ascorbate is ascorbate monoanion, $AscH^{\bullet-}$) leaving behind the ascorbyl radical ($Asc^{\bullet-}$). Reaction 10: The regeneration of Vitamin E by GSH: the oxidized Vitamin E radical ($T\text{-}O^{\bullet}$) is reduced by GSH. Reaction 11: The oxidized glutathione (GSSG) and the ascorbyl radical ($Asc^{\bullet-}$) are reduced back to GSH and ascorbate monoanion, $AscH^{\bullet-}$, respectively, by the dihydrolipoic acid (DHLA) which is itself converted to ≷-lipoic acid (ALA). Reaction 12: The regeneration of DHLA from ALA using NADPH. Reaction 13: Lipid hydroperoxides are reduced to alcohols and dioxygen by GPx using GSH as the electron donor. Lipid peroxidation process. Reaction 14: Lipid hydroperoxides can react fast with Fe^{2+} to form lipid alkoxyl radicals ($LO^{\bullet}$), or much slower with Fe^{3+} to form lipid peroxyl radicals ($LOO^{\bullet}$). Reaction 15: Lipid alkoxyl radical ($LO^{\bullet}$) derived for example from arachidonic acid undergoes cyclisation reaction to form a six-membered ring hydroperoxide. Reaction 16: Six-membered ring hydroperoxide udergoes further reactions (involving ≷-scission) to from 4-hydroxy-nonenal. Reaction 17: 4-Hydroxynonenal is rendered into an innocuous glutathiyl adduct (GST, glutathione-*S*-transferase). Reaction 18: A peroxyl radical located in the internal position of the fatty acid can react by cyclisation to produce a cyclic peroxide adjacent to a carbon-centred radical. Reaction 19: This radical can then either be reduced to form a hydroperoxide (reaction not shown) or it can undergo a second cyclisation to form a bicyclic peroxide which after coupling to dioxygen and reduction yields a molecule structurally analogous to the endoperoxide. Reaction 20: Formed compound is an intermediate product for the production of malondialdehyde. Reactions 21, 22 and 23: Malondialdehyde can react with DNA bases cytosine, adenine, and guanine to form adducts M1C, M1A and M1G, respectively.

from the increased production of ROS, inactivation of detoxification systems or excessive consumption of antioxidants, is a causative factor in the oxidative damage of cellular structures and molecules, such as lipids, proteins and nucleic acids (Kehrer, 1993; Harman, 1998). The peroxidation of polyunsaturated fatty acids leads to conjugated dienes (CD) formation, followed by the cleavage of the fatty acid chains and subsequent release of the reactive aldehydic products, i.e., malondialdehyde, 4-hydroxy-2,3-transnonenal, 4-hydroxy-2,3-transhexenal, often referred to as thiobarbituric acid-reacting substances (TBARS) (Janero, 1990; Kehrer, 1993). Biological membranes rich in unsaturated fatty acids are cellular structures susceptible to free radical attack (Halliwell and Gutteridge, 1984; De Zwart et al., 1999). Proteins are also sensitive to oxidative damage that leads to alteration in their structure and ability to function (De Zwart et al., 1999). Protein oxidation can lead to a loss of critical thiol groups (SH) in addition to modifications of amino acids leading to the formation of carbonyl and other oxidized moieties (Radi et al., 1991; Kehrer, 1993; Preedy et al., 1998). The interaction of reactive oxygen species with other cellular macromolecules such as DNA results in an impairment of the genetic material in the cell nucleus (De Zwart et al., 1999). The reactive nature of oxygen and its intermediates is also considered to participate in autoimmune diseases of endocrine glands such as some thyroid disorders (Sundaram et al., 1997). Increased oxidative stress may result from an over production of precursors of reactive oxygen radicals and/or a decreased efficiency of the inhibitory and scavenger system (Konukoğlu et al., 1998). The oxidative stress appears to represent a portion of a cascade of biochemical changes leading to CNS dysfunctions. Thus, the pathways of ROS formation, the lipid peroxidation process and the role of glutathione and other antioxidants (Vitamin E, Vitamin C, lipoic acid) in the management of oxidative stress (equations are not balanced) as a following in Fig. 11 (Valko et al., 2007).

In addition, hypothyroidism was found to be associated with marked oxidative stress, one of the earliest manifestations of which was a decline in the level of glutathione (Rahaman et al., 2001). Glutathione (GSH; γ-L-glutamyl-L-cysteinyl glycine), the ubiquitous thiol-containing tripeptide, being part of an integrated antioxidant system of the cells, is a major free radical scavenger and a highly sensitive indicator of cell function and viability. The first and rate-limiting step in GSH biosynthesis is catalyzed by glutamate cysteine ligase (GCL) [gamma-glutamyl synthetase (γ-GCS); EC 6.3.2.2] a heterodimeric enzyme consisting of the larger catalytic subunit (GCLC) and smaller modulator subunit (GCLM) that catalyzes the formation of γ-glutamyl cysteine, which is under nonallosteric feedback inhibition by GSH (Richman and Meister, 1975). The genes for the two subunits of GCL are located on separate chromosomes both in humans and in mouse (Sierra-Rivera et al., 1995; Tuschiya et al., 1995; Sierra-Rivera et al., 1996). GCLC contributes all the enzymatic activity and is feedback inhibited by GSH while GCLM increases the catalytic efficiency of the holoenzyme under physiological conditions by decreasing the apparent Km for the substrate glutamate and increasing its apparent Ki for GSH (Huang et al., 1993). While GCL is the key enzyme involved in the synthesis of GSH, the degradation of GSH is catalyzed by the astroglial ecto-enzyme, γ-glutamyl transpeptidase (γ-GT) which transfers the γ-glutamyl moiety of GSH to an acceptor amino acid (Meister et al., 1981). TH stimulates GSH by up regulating the activity of GCL, the rate-limiting enzyme in GSH biosynthesis. Several lines of evidences support this finding (Dasgupta et al., 2007): (a) First, developing hypothyroid cerebra of postnatal ages 5–20 have significantly less GCL activity than their age-matched normal controls. This pattern of fall in GCL activity is closely parallel to alterations in the level of GSH in hypothyroid cerebra of corresponding ages (Dasgupta et al., 2005). (b) Second, administration of TH to the hypothyroid animals up regulated cerebral GCL activity. (c) Third, astrocytes cultured in TH-depleted media up regulated their GSH level in response to T3 and this up regulation is completely inhibited by L-buthionine *S*,*R*-sulfoximine—a specific inhibitor of GCL. The main protective roles of glutathione against oxidative stress are (Masella et al., 2005): (1) Glutathione is a cofactor of several detoxifying enzymes against oxidative stress, e.g., glutathione peroxidase (GPx), glutathione transferase and others. (2) GSH participates in amino acid transport through the plasma membrane. (3) GSH scavenges hydroxyl radical and singlet oxygen directly, detoxifying hydrogen peroxide and lipid peroxides by the catalytic action of glutathionperoxidase. (4) Glutathione is able to regenerate the most important antioxidants, Vitamins C and E, back to their active forms; glutathione can reduce the tocopherol radical of Vitamin E directly, or indirectly, via reduction of semidehydroascorbate to ascorbate (Fig. 11; Valko et al., 2007). The capacity of glutathione to regenerate the most important antioxidants is linked with the redox state of the glutathione disulphide-glutathione couple (GSSG/2GSH) (Pastore et al., 2003).

Astrocytes constitute the major components of the mammalian CNS, outnumbering neurons by many fold in adult brain (Dasgupta et al., 2007). In addition to various supporting functions like guiding neuronal migration and maintaining the microenvironment of neurons, astrocytes play a constitutive role in the formation of the blood–brain barrier (Janzer and Raff, 1987), represent the major glycogen depots of brain (Cataldo and Broadwell, 1986), support immune defense by producing various immunoactive cytokines (Benveniste, 1992), maintain the external potassium concentration (Walz and Hertz, 1983), and perform many other important functions. In addition, astrocytes protect neurons against oxidative stress via transcriptional up regulation of the glutathione synthesis (Iwata-Ichikawa et al., 1999). Astrocytes appear to contain higher GSH levels than neurons both *in vivo* (Rice and Russo-Menna, 1998) and in culture (Dringen et al., 1999) and play an important role in the maintenance of cerebral glutathione homeostasis as well as in the protection of the brain against oxidative stress (Dringen, 2000). In coculture, astrocytes support other brain cell types in the defense against ROS (Desagher et al., 1996). In the presence of astroglial cells, neurons are protected against the ROS-induced toxicity of various compounds and treatments (Langeveld et al., 1995; Desagher et al., 1996). It has been suggested that *in vivo*, a

compromised astroglial glutathione system may contribute to a lower defense capacity of the brain against ROS and subsequently to increased susceptibility to ROS of astrocytes themselves and of neighboring cells (Dringen, 2000). The synthesis of GSH in neurons is facilitated by astrocytes, which provide the precursor cysgly for the synthesis of GSH in neurons. Cysgly is generated from extracellular GSH by the exopeptidase, γ-GT of astrocytes (Dringen et al., 1997) and is utilized efficiently in micromolar concentrations by neurons (Dringen et al., 1999). Additionally, astrocytes also release glutamine (Hertz et al., 1999) which together with cysgly provides neurons with all three constituent amino acids of GSH. Recent studies on the effect TH on the glutathione-metabolizing enzyme, γ-GT, in developing normal and hypothyroid cerebra and in astrocyte cultures suggested that TH stimulates the enzyme (Dasgupta et al., 2005). The products of γ-GT reaction are putative precursors of neuronal GSH (Dringen, 2000; Dringen et al., 2000; Dringen and Hirrlinger, 2003). Thus, the increased γ-GT activity in the astrocytes could provide a mechanism for the synthesis and maintenance of neuronal GSH, thus protecting them from oxidative stress. However, since the stimulation of γ-GT by TH was incompatible with the down-regulation of GSH in the hypothyroid cerebra (Rahaman et al., 2001; Dasgupta et al., 2005), it was suggested that enzymes other than γ-GT, involved in the biogenesis of GSH, might be responsible for the regulation of GSH by TH in the developing brain. The overall results suggest that TH plays a positive role in maintaining GSH homeostasis in astrocytes and in protecting the brain from oxidative stress as well as protection of the brain from pathophysiological conditions involving oxidative stress.

On the other hand, previous studies have indicated an imbalance between oxidant/antioxidant status and enhanced oxidative stress in hyperthyroidism (Sundaram et al., 1997; Abalovich et al., 2003; Bednarek et al., 2004a,b). Abalovich et al. (2003) indicated an increase in oxidative stress markers and a decrease in markers of the antioxidant system in hyperthyroid patients with Graves' disease (GD). In their study, treatment with MMI led to a decrease in oxidative stress markers and an increase in antioxidant system activity. Increased TBARS concentrations indicated an increase in lipid peroxidation, which results from increased free radical generation in GD (Ademoğlu et al., 2006). Previous studies have also indicated increased concentrations of oxidative stress markers in plasma and/or other tissues of hyperthyroid patients (Komosinska-Vassev et al., 2000). Ademoğlu et al. (2006) found that, in euthyroid Graves patients treated with antithyroid drugs, TBARS were significantly elevated and total thiol (t-SH) concentrations were significantly decreased compared with euthyroid controls. Therefore, even in the euthyroid state, GD leads to an increase in oxidative stress. Increased oxidative stress may play a role in the pathogenesis of GD (Carnell and Valente, 1988; Reid and Wheeler, 2005). Consequently, markers indicating increased oxidative stress may be observed in GD patients, even in the euthyroid state. Higher plasma and tissue GPx concentrations may indicate a compensatory increase in the antioxidant defense mechanism (Ademoğlu et al., 2006). The previous authors suggested that the increased activity of the enzymes of the antioxidant defense system (GPx and SOD) and the increased t-SH concentrations in thyroid tissue indicate the reactive response to increased free radical generation. The compensatory increase in the antioxidant system may lead to neutralization of oxidative damage at the tissue level.

Moreover, oxidative stress plays an important role in hyperthyroidism-induced tissue damage, as well as in development of autoimmune disorders (Bednarek et al., 2004a). Also, Abalovich et al. (2003) confirmed the imbalance of the antioxidant/oxidant status in hyperthyroid patients. In man, hyperthyroidism is characterized by significant changes in circulating parameters related to oxidative stress, including: (1) increased levels of TBARs (Videla et al., 1988; Ademoglu et al., 1998; Seven et al., 1998; Adali et al., 1999; Bianchi et al., 1999; Sewerynek et al., 2000; Komosinska-Vassev et al., 2000; Guerra et al., 2001; Yavuz et al., 2004) and conjugated dienes (Komosinska-Vassev et al., 2000; Sewerynek et al., 2000); (2) elevated levels of H_2O_2 and lipid hydroperoxides (Bednarek et al., 2004b); and (3) reduced levels of thiols (Wilson et al., 1989; Adali et al., 1999; Komosinska-Vassev et al., 2000), ascorbic acid (Ademoglu et al., 1998; Seven et al., 1998), α-tocopherol (Ademoglu et al., 1998; Bianchi et al., 1999), and coenzyme-Q (Bianchi et al., 1999). Further studies are needed to emphasize the role of oxidative stress markers as indicators of hyperthyroidism. Thus, we can suggest that there is increased susceptibility to peroxidative-induced damage associated with thyroid dysfunction (hypo- or hyperthyroidism).

Actually, thyroid hormone formation requires the coincident presence of peroxidase, H_2O_2, iodide, and acceptor protein at one anatomic locus in the cell (Degroot and Niepomniszcze, 1977). Both thyroglobulin and iodide are substrates for this organification reaction that is catalyzed by thyroid peroxidase (TPO). TPO first oxidizes iodide to iodine and then iodinates tyrosines on thyroglobulin to produce monoiodotyrosine and diiodotyrosine, and finally links two iodinated tyrosines to produce T4 and T3 (Jahnke et al., 2004). However, for several decades, TPO has no activity without a source of H_2O_2 (Taurog, 1974). In several species, the regulation of thyroid oxidase (THOX) expression has been studied after forskolin and TSH stimulation. In pig, rat and dog thyroid cells cultures, the addition of forskolin leads to upregulation of THOX mRNA. This effect is less pronounced for human thyroid cells. Methimazole treatment results in TSH increase and THOX2 downregulation in rats. (Dupuy et al., 1999, 2000; De Deken et al., 2000). There is no difference in THOX immunostaining in thyroid cancer tissues obtained in the same patient in both eu- and hypothyroid conditions, also suggesting that *in vivo* high TSH levels do not increase THOX expression in human thyroid (Lacroix et al., 2001). Regulation of expression differs from the sodium iodide symporter in multinodular goiter, hypofunctioning adenomas and hyperfunctioning thyroid tissues (Caillou et al., 2001). There is a direct (inhibitory) effect of iodide and iodocompounds on the enzymatic activity of the thyroid NADPH oxidase (Ris-Stalpers et al., 2002). Several groups have studied the biochemical mechanism of H_2OO_2O genera-

tion. However, there are scant reports on goiter and hypothyroidism in relation to decreased thyroidal H_2O_2 generation (Niepomniszcze et al., 1987; Figueiredo et al., 2001). Also, Dasgupta et al. (2007) said that the delay in the development of cerebral oxidative enzymes might due to the reduction in succinic dehydrogenase and glutamic dehydrogenase activity Ğ markers for nerve terminal development. Peroxidase is typically elevated in thyroid tissue from patients with hyperthyroidism, sometimes deficient in cold thyroid nodules, and frequently diminished in tissue from patients with Hashimoto's thyroiditis (Degroot and Niepomniszcze, 1977).

The above results presumed that, the thyroid-antioxidant system interactions could protect the cells and tissues, in general, during the development from the harmful effect of ROS. Thus, the disturbance in the pro/antioxidant system due to the thyroid dysfunction might be the cause of the partial retardation in CNS-neurons and general growth. Taken together, the results are suggestive of the imbalance of generation and scavenging of free radicals play an important role in determining tissue damage associated with thyroid alterations.

13. Final remarks

In general, thyroid hormones have some actions that might be useful therapeutically, but others that are deleterious. Potential therapeutically useful actions include those to induce weight loss and lower plasma cholesterol levels. Potential deleterious actions are those on the heart to induce tachycardia and arrhythmia, on bone to decrease mineral density, and on muscle to induce wasting.

It is worth mentioning that, together with the previous studies, the current review throw up a number of important findings. Thyroid hormones are a key regulatory factor of the brain developmental program. During development, the role of thyroid hormone is the coordination of seemingly unrelated maturational processes. These processes are influenced by the hormone only temporarily during overlapping windows of development with regional specificity. The cellular basis for these effects lies in the organizational role of TH in neuronal migration, synaptogenesis and differentiation of multiple cell types. Thus, any vigorous changes in the thyroid hormones levels during the critical periods of the development may cause a serious damage to the structural development and organization of the brain, and irreversible morphological and cytoarchitecture abnormalities including altered cell migration, delay in maturation of neurons and glial cells, reduction of synapses, myelination deficits, changes in the number of particular cell populations. Hyper- or hypothyroidism may affect directly or indirectly the neuronal and glial cell types and lead to disruption in the interactions of thyroid with neurotransmitters, GABA, adenosine and pro/antioxidant systems during CNS development. Lastly, this severe effect may be responsible for the loss of neurons vital functions and may lead, in turn, to the biochemical dysfunctions (pathophysiology) and the reverse is true. Because signs of nervous system dysfunction develop in hypothyroid and hyperthyroid

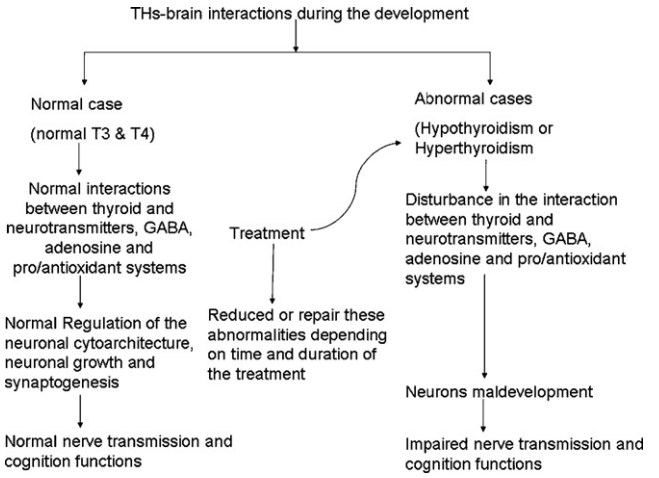

Fig. 12. The normal and abnormal thyroid states interactions with the brain development.

individuals, it is possible that even relatively small deviations of brain iodocompound economy can produce significant changes in behavior and autonomic nervous system function. We summarized the previous findings in the following Fig. 12. We hope this review will serve the purpose not only of summarizing the different states of thyroid hormones on CNS development but also of illuminating gaps in our knowledge such as those mentioned.

14. Future direction

The resolution of this issue will require additional evidence at a molecular level either demonstrating a direct action of the thyroid hormones on the fetal brain or additional evidence supporting the suggestion that the observed effects of maternal hypo- or hyperthyroidism on fetal development are explained by impaired gestation. Thus, whether the adverse effects of maternal hypo- or hyperthyroidism on fetal development are mediated directly by loss of the maternal hormones contribution to the fetus, indirectly by metabolic impairment of gestation, or both. In addition, future attention should be focused on identifying a nongenomic approach because of there is scant evidence and these actions of TH differ across the developmental time and brain region.

More information is needed to determine which environmental chemicals interact with the thyroid hormone system and to understand the site and mechanism of action of these environmental chemicals during brain development. Thus, it is critical to improve animal models of thyroid disruption as well as advance our ability to translate animal data to human risk. To accomplish this goal it is important to increase the use of "-omics" technology (e.g., toxicogenomics, proteomics and metabonomics), develop and use new imaging technologies, develop and use genetic models of thyroid hormone receptor defects or deficiency, and increase multidisciplinary and interdisciplinary research projects. Furthermore, studies are required to identify any variations or polymorphisms in elements of the pathway of thyroid hormone action, e.g., T3/rT3 ratio, deiodinase or transporter polymorphisms which

predict the psychological response to thyroid hormone or correlate with other potentially thyroid hormone related effects (eg sleep parameters, echocardiographic changes or changes in bone turnover).

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