REVIEW

EFFECTS OF THYROID HORMONES ON CENTRAL NERVOUS SYSTEM DEVELOPMENT

Ali Süha ÇALIKOĞLU, M.D.

The University of North Carolina at Chapel Hill, Department of Pediatrics, Division of Endocrinology, U.S.A.
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SUMMARY :

Thyroid hormones are essential for normal brain development. The most striking effects of the absence of thyroid hormones occur during maturation of central nervous system. In man, congenital hypothyroidism leads to multiple morphological and biochemical alterations resulting in irreversible mental retardation. Early diagnosis and hormonal replacement treatment, however, can reverse these consequences. Because clinical findings of congenital hypothyroidism in the perinatal period are subtle, neonatal screening programs have been developed and one-third of the world population is currently screened for the disease. Most of the information about the disease has been obtained from animal studies. Reduced myelination, poor neuritic outgrowth and dendritic arborization are among the changes in brain caused by congenital hypothyroidism. We have demonstrated that congenital hypothyroidism delays the formation and retards the growth of mouse primary somatic sensory cortex, indicating an important role for the thyroid hormones in the cerebral cortical organization in mammalian brain. However, we have yet to define the mechanisms of thyroid hormone action in brain development. It is likely that some of the actions of thyroid hormones in brain are mediated by local growth factors, such as nerve growth factor and insulin-like growth factor-I.

Key Words : *Brain, Thyroxin, Thyroid Hormone, Cell Differentiation.*

INTRODUCTION

Thyroid hormones (TH) have been known to be important for normal brain development for years (Table 1). Although Paracelsus described the association of endemic goiter and cretinism in 16th century, the casual relationship between the thyroid gland and cretinism was not recognized until the end of the 19th century. The discovery of thyroid extract therapy by Sir William Osler in 1898 was self-described as a triumph of experimental medicine. He wrote "Within six weeks, a poor feeble minded toad like caricature of humanity may be restored to mental and bodily health"(1). Untreated congenital hypothyroidism has major effects on neurological development, and the severity of the effects are correlated with the magnitude and the apparent time of onset of the deficiency (prenatal vs. postnatal) and the age at which appropriate replacement therapy is begun (see reviews 2, 3).

Early diagnosis and hormonal replacement in cretins is essential for achieving therapeutic

Table 1 : Thyroid hormone action on the developing central nervous system.

Thyroid hormones;
* increase the rate of neuronal proliferation in the cerebellum
* act as the "time-clock" to end neuronal proliferation and stimulate differentiation
* control the organization pattern of cerebral cortex and cerebellum
* stimulate the formation and development of neuronal processes
* are important for normal formation, function, and stability of cytoskeletal system of neurons
* induce neuronal maturation and myelinization

success, a fact that was recognized as early as 1915 and has been verified many times. It has been found that administration of thyroxin (T4) during the early neonatal period significantly improves the intellectual capacity. Beginning therapy after 4 months of age is associated with a poor mental prognosis that is nearly identical to untreated cases (4, 5) (Fig. 1). These observations led to three very important conclusions:

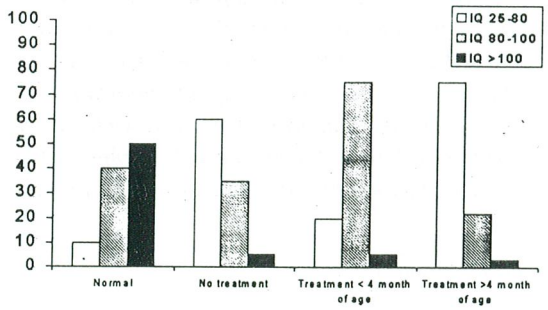

Fig. 1 : Relationship of age at onset of thyroid treatment to subsequent IQ in patients with congenital hypothyroidism. Note that the vast majority of untreated patients with congenital hypothyroidism had an IQ <80 as did patients in whom replacement treatment was started after 4 months of age. Treatment before 4 months of age prevents severe mental retardation, although the majority of patients had an IQ of 80-100 (4, 5).

1. The diagnosis of congenital hypothyroidism should be made and treatment begun as early as possible.

2. The clinical findings early in the course of the disease are minimal and early diagnosis based on clinical findings is very difficult in the neonatal period; therefore, neonatal screening programs for congenital hypothyroidism were developed in 1971 and have been expanded to almost one-third of the world population since that time (2).

3. There is a critical period in which thyroid hormones are essential for brain development. This critical period is at least the first three months of life in humans.

After 25 years of experience, it is clear that screening programs are successful in the detection and early treatment of infants with hypothyroidism (6-8). Studies of mental and motor development have shown a mild decrease in IQ in infants with congenital hypothyroidism compared to controls in spite of early and appropriate treatment (6, 9). These studies also report a higher frequency of delay in motor skills, poor coordination, delayed speech and learning problems (9). In some infants, therefore, the effects of hypothyroidism can not be completely prevented by early detection and treatment. Furthermore, the critical period for thyroid hormones appears to span the last two trimester of human gestation.

Efforts to understand the mechanisms of the hormonal effect have been hampered by the enormous complexity of the brain which is made up of 100 billions of cells and 100 trillions of synapses. Nonetheless, the relationship between thyroid hormones and brain development is one of the best-studied areas of neuroscience. An enormous amount of clinical data is available to understand the consequences of the disease and the relationship between the timing and adequacy of treatment and

neurological sequelae of the disease. Histopathological data in human, however, is sparse (1).

Validation of animal models to study thyroid hormone action in brain development

Animal models have been used to study the influence of thyroid hormones on neurological development. Rodents appear to provide an adequate model of thyroid hormone actions, but assumptions must be made regarding comparable developmental stages. For example in rodents, brain development at birth is delayed compared to human newborns and ten-day-old rat brain is comparable in maturation to that of man at birth. The rat brain at birth is at a similar stage as the human brain at 5-6 months of gestation (10, 11). Consequently, the stage of brain development in the last trimester of human development occurs postnatally in the rat. These differences facilitate manipulation of nutritional and endocrine environment of the developing rat brain during this important period.

Prenatal Development of Thyroid Functions

In man, thyroid hormone synthesis begins at 10-12 weeks of gestation as judged by the appearance of colloid in the fetal thyroid. At 12 weeks of gestation low levels of T4 can be detected in the serum and they increase rapidly during gestation. Serum T3 is detectable by 15 weeks and, like T4, increase progressively during gestation. Serum TSH is measurable at 12 weeks and also increased steadily. Likewise a steady increase in fetal serum thyroxin binding globulin is seen during gestation (12-14, see also review: 15, 16).

Central Nervous System Development and Thyroid Functions

When the development of the nervous system is viewed with respect to the influence of thyroid hormones, three developmental periods can be defined (see review: 17). Phase I 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. Any exposure of the brain to thyroid hormones during this period must come from the mother and it is not known if thyroid hormones play a direct role in neurological development in this period. Most of the brain stem and a significant portion of cerebral neurogenesis occur during phase I. Neuronal migration also occurs during phase I, but significant neuronal maturation, neurite formation and synaptic development in the forebrain has not yet begun.

Phase II spans the second and third trimester of human gestation and the last four days of rat gestation. 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.

Phase III is the period after birth. During this period the brain is dependent upon thyroid hormones secreted by the neonate's thyroid. This phase in rats encompasses a period when much of neuronal proliferation, migration and differentiation occurs 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. Because the human brain at birth is at a later developmental stage than of the rat, much of the cerebellar neuronal proliferation migration and differentiation in human occurs in phase II (but continue into phase III). In man, myelination begins in phase II, but most gliogenesis and myelination occurs after birth in phase III.

Morphogenetic actions of thyroid hormones

Cerebral cortex

Thyroid hormones do not appear to influence the differentiation or the number of the neurons. In a hypothyroid rat, however, neuron density is increased and cell body size is reduced. In addition, there is a decrease in the density of axon terminals (especially in layer IV which received specific thalamic afferents) and a reduction in the growth and branching of the dendrites of pyramidal neurons (18). The dendritic and axonal deficiencies are estimated to lead to a greater than 50% decrease in dendrite and axonal interactions. These findings indicate that the decrease in brain size in congenitally hypothyroid rats results from an increase in cell packing rather than a decrease in cell number (19).

Thyroid hormones play and important role in the organization of the cerebral cortex. We have

demonstrated that congenital hypothyroidism delays the formation and retards the growth of mouse primary somatic sensory cortex (S1) indicating that thyroid hormones participate in the timing of S1 formation, and that thyroid hormones regulate its relative size by modulating the developmental timing of area specification and brain growth (20) (Fig. 2).

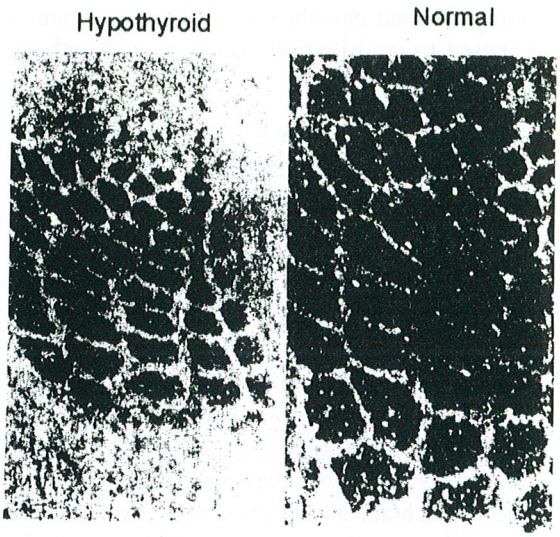

Fig. 2 : The posteromedial barrel subfield (PMBSF) in hypothyroid and normal mice. Photomicrographs from cytochrome oxidase-stained tangential sections throughout layer IV of somatosensory cortex (S1). Note that cross-sectional area of barrel and PMBSF is markedly reduced in hypothyroid mice while the number and shape of the PMBSF barrels are comparable (20).

S1 contains a representation of the body surface formed by anatomic modules termed barrels where thalamic and brain stem afferents synapse with cortical neurons. Each barrel thus represents discrete collections of peripheral mechanosensory receptors. PMBSF is a portion of the trigeminal thalamo-cortical pathway (TThC). In rodents the TThC is responsible for transmitting tactile information from facial whiskers to the cerebral cortex. Each of 34 PMBSF barrels is the representation of a single whisker in the facial whisker pad. These 3-dimensional barrel structures are composed of a cell dense wall surrounding a hollow that is predominantly composed of neural connections among axon terminal fields from ventroposteromedial thalamic nucleus neurons and cortical layer IV dendrites. Barrel dimensions, therefore, correlate with changes in the numbe of neurons and the complexity and the number of their connections.

Cerebellar cortex:

The cerebellar cortex is more convenient for the study of thyroid hormone's morphogenetic actions on the CNS, because its anatomy is relatively simple and its development is relatively late (making it readily available for study). In the rat, about 97% of the cerebellar cells are formed during postnatal life (19). Most proliferating cells, i.e. granule cells, originate in the external granular layer (EGL) and then migrate inward through to molecular layer to internal granular layer. These dramatic events provide a convenient opportunity of studying the effects of thyroid dysfunction on the formation, maturation and migration of cerebellar neurons (21).

In hypothyroid rats the duration of the proliferative phase is prolonged. As a result, EGL persists beyond the normal age of 21 days. This results in a cerebellum with normal cell number but altered composition, with fewer basket cells, more glial cells and a normal number of granule cells (22). The maturation of Purkinje cells is also delayed in hypothyroid rats. The growth and branching of their dendritic arborization, as well as ontogenesis of their dendritic spines is markedly retarded. In addition, the axons of granule cells, the density of synapses in the molecular layer and the differentiation of the cerebellar glomeruli are retarded and abnormal (22).

Exposure of the rat to excess T4 at birth increases the rate of cellular proliferation in the cerebellum because the G phase of mitosis is shortened, resulting in a transient increase in the total number of cells (23). The excess in T4, however, terminates cellular proliferation prematurely and the total number of cells seen in mature brain is decreased. Based on these findings, thyroid hormones have been proposed to time the termination of proliferation and to stimulate differentiation (24). Despite these alterations, cerebellar development follows essentially normal sequences.

Biochemical actions

Hypothyroidism causes a decrease in the brain protein and RNA synthesis. In fact it has been proposed that the mechanism of impaired neurological development in hypothyroidism may be through its role as a regulator of protein synthesis. Thyroid hormones have also been shown to regulate transcription of specific mRNAs and to alter gene expression. The latter is proposed as the mechanism whereby thyroid hormones control brain development. Thyroid hormone's influence on protein synthesis may be mediated by increasing amino acid transport into brain cells, by stimulating the synthesis of ribosomes (and thus their function

in translation), and/or by altering mRNA stability (25).

The biochemical maturation of the brain is delayed in hypothyroidism. This includes retarded development of the capacity to convert glucose carbons into amino acids – an index of neuronal process development; reduction in succinic dehydrogenase and glutamic dehydrogenase activity – markers for nerve terminal development; retarded development of cerebral oxidative enzymes. Finally when neonatal rats are thyroidectomized, there is a decrease in amino acid incorporation into protein and a decrease in RNA synthesis (19, 26, 27).

Thyroid hormones regulate gliogenesis and myelinogenesis (10, 26). Neonatal hyperthyroidism accelerates while hypothyroidism delays the deposition of myelin (28). Additionally in hypothyroid animals, the lipid composition of myelin is markedly reduced, and myelin structure of the myelin is altered (29). 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 (30).

Thyroid hormones are also known to regulate neuronal outgrowth and synapse formation (31). The inability of hypothyroid neonates to show normal neuronal outgrowth is thought to be a result of abnormalities in the development of cellular cytoskeleton. 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 (17, 25). Thyroid hormones regulate the gene expression of the brain tubulin MB5 and M1 mRNA isotopes in perinatal mouse (32). Thyroid hormones also regulate the expression of two specific microtubule-associated proteins, tau and MAP2, which promote tubulin polymerization and function as linkers between microtubules and cytoskeleton. Perinatal thyroid hormone deficiency has been shown to decrease the delivery of cytoskeletal proteins to developing terminals via the slow component of axonal transport (33). Such changes in formation, transport and function of components of the cytoskeleton could cause the observed impairment of neuronal process outgrowth.

Interaction of Thyroid Hormones with Tissue Growth Factors in Central Nervous System

The above described molecular and neuroanatomical events that are influenced by thyroid hormone may occur as a direct effect of thyroid hormone or as a secondary effect mediated by second messengers that are regulated by thyroid hormone, such as growth factors. Growth factors such as epidermal growth factor (EGF), nerve growth factor (NGF) and insulin-like growth factors (IGF) have been proposed to play important roles in neurological development. Likewise, thyroid hormones have been proposed as regulators of these agents.

Thyroid hormones are known to interact with several growth factors including IGF-I, EGF and neurotrophins. There are, however, few studies of the interaction among IGF system proteins and thyroid hormones during brain development (34). Although no research demonstrates any change in IGF-I mRNA with altered thyroid hormone status, serum IGF-I levels are low in children with hypothyroidism and normalize after thyroid hormone replacement (35, 36).

The interaction between neurotrophins and thyroid hormones has been studied in relatively more detail. Neurotrophins are responsible for the survival and differentiation of defined neuronal populations during CNS development and thus contributes to the formation of complex cellular networks. Their biological properties make them good candidates for the mediation of thyroid hormone action. Hypothyroidism induces changes in the concentration of some neurotropins. NGF mRNA is reduced in the cortex, hippocampus and cerebellum and its receptor TrkA is lowered in the striatum in hypothyroid rat. Neither BDNF, TrkBnor TrkC appear to be influenced by thyroid hormone deficiency (37).

Control of neurotrophin expression appears to be a major mechanism in the regulation of Purkinje cell differentiation by thyroid hormones. In vitro Neurotrophin 3 induces morphological differentiation of immature Purkinje cells whereas T3 alone has no effect. Both in vitro and in vivo T3 induces an increased production of neurotrophin-3

by cerebellar granule cells. Because Purkinje cells express the neurotrophin-3 receptor TrkC, T3 may induce Purkinje cell differentiation by acting indirectly to increase neurotrophin-3 production by granule cells (38, 39).

Interaction of Fetal and Maternal Thyroid Functions

For years the placental transport of thyroid hormones has been debated. Because the human fetal thyroid gland and pituitary-thyroid axis becomes functional late in the first trimester (before the time of fetal thyroid function), thyroid hormone exposure in the first trimester must come from the maternal circulation via placental transport. The presence of thyroid hormones in coelomic and amniotic fluid prior to onset of fetal thyroid function provides evidence of placental transfer in the first trimester. Furthermore, the coelomic fluid T4 concentration varies directly with the maternal serum T4 concentration (40). During the second and third trimesters, there is a marked maternal to fetal gradient of free T4 and T3 (41). For example, at delivery maternal serum free T3 concentrations are twice those in cord serum (42). Newborn infants with thyroid hormone agenesis or those with complete defects in thyroid hormone synthesis have cord serum f4 concentrations between 20-50% of normal infants (43). These observations, and others in rats, indicate that maternal-fetal transfer of thyroid hormones occurs, albeit at a relatively low level. The importance of even small quantities of maternal thyroid hormones during critical periods of fetal brain development, however, cannot be ignored and raise the question of whether these relatively small amounts of thyroid hormone minimize the effects of fetal hypothyroidism.

Complex enzymatic systems regulate the availability of thyroid hormones in different tissues and these systems may maximize the effects of a limited amount of thyroid hormone in vital tissues such as brain.One such system is composed of three enzymes that catalyze the deiodination of iodothyronines. In man, Type I deiodinase is expressed in liver, kidney, thyroid and pituitary gland, and is responsible for most of the T3 in serum. Type II deiodinase is expressed in brain, pituitary gland, brain, adipose tissue and placenta. Type III deiodinase is present in high amounts in placenta and epidermis (12, 14). The ontogeny of these three deiodinases differs in the developing fetus. Type II and Type III appear at mid-gestation, but Type I is not evident until late in gestation. Type II deiodinase activity increases in the fetus with hypothyroidism, whereas Type I and Type III deiodinase activity decreases. Because Type II deiodinase is present mainly in brain tissue, these ontogenic changes appear to enhance shunting of T4 to brain tissues(44-46).

Another metabolic way may enhance or preserve thyroid hormone action in hypothyroid fetus. Thyroid hormones can be inactivated by sulfation and the resultant hormones do not bind to nuclear T3 receptors (47). Fetal brain and liver tissue, however, have sulfatase activity and desulfation of T3 sulfate to T3 in fetal liver and brain increases available T3 in fetal brain (48).

Although fetal thyroid development is largely independent from maternal influences, the above systems appear to protect the fetus with hypothyroidism by maximizing the use of limited transfer of thyroid hormone from mother to fetus. For example, it has been shown that in hypothyroid rat fetuses with hypothyroidism, Type II deiodinase activity is increased and leads to a normalization in brain T3 concentrations (45, 50).

Conclusions

Thyroid hormones are essential for normal neonatal development in both humans and rodents. Data obtained in follow-up studies of neonatal hypothyroidism screening programs suggest that fetal thyroid hormones are important for normal fetal brain development late in gestation. Experimental data indicate that thyroid 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. The finding that thyroid hormone receptors are expressed in the brain during early gestation further suggests that thyroid hormones have effects at this period. Clinical data indicate that maternal hypothyroidism leads to significant neurological impairment, even if it is corrected in the second trimester and neonates are treated in early postnatal life. These findings suggest that thyroid hormones are also important for normal brain development during the first half of gestation.

Despite the presence of enormous amount of information about the influences of thyroid hormone on the central nervous system development, there are still many unanswered questions (51). The mechanism of the effects of this "old-fashioned" hormone and its interaction with growth factors is a challenge for basic researchers. We hope that the efforts of basic researchers will motivate the clinicians to be more concerned about prevention of small but significant neurological consequences due to impaired or subnormal maternal thyroid functions.

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Correspondence to : Dr. Ali Süha ÇALIKOĞLU
CB#7220, 509 Burnett-Womack
Chapel Hill, NC 27599-7220, U.S.A.
Phone : 1-919-966-4435 Ext.241
Fax : 1-919-966-2423
E-mail: asc@med.unc.edu

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