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***Research paper***



# Influence of thyroid hormones on nervous system development – brief review

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**Abstract**

The thyroid gland secretes important hormones for the overall development of organism, which include some related to tissue growth, as well as hormones that stimulate the O2 uptake in the cells and help the regulation of lipid and carbohydrate metabolism. Therefore influence the body mass and activity level thereof, including the activities of nervous system. The thyroid gland is not essential for life, however their absence or hypofunction during fetal and neonatal life result in severe mental, physical and mental slowness, poor resistance to cold, as well as dwarfism. The hyperfunction of this gland leads to weight loss, nervousness, tachycardia, tremor and production of excess heat.

***Keywords***: *Brain Development; Potassium Iodide; Supplements; Thyroid Hormones.*

## 1. Morphological considerations

This glandular tissue derives embryologically from the stomodeum pharyngeal pouch and migrate from the thyroglossal duct to the neck, where is lodged. It has two morphological horns joined by an inferior isthmus, being suspended by a fascia against the first tracheal rings [1]
This tissue is part of the endocrine system, which comprises a series of glands that secrete substances known as hormones into the bloodstream. Among these secreted substances, there are certain hormones that help increasing the consumption of oxygen by the cells, and the metabolism of lipids and carbohydrates [2].
This gland has a large amount of follicles filled with substance colloid therein, being these cells responsible for synthesize and secrete a protein called thyroglobulin in these follicles [3]. Each thyroglobulin molecule contains the amino acid tyrosine in its composition, which is the basis for construction of thyroid hormones [4].

## 2. Formation and secretion of thyroid hormones

The synthesis of thyroid hormones is directly dependent on iodine and involves three basic steps [5]. First, iodine is absorbed on diet by digestory tract e transported by proteins of basal membrane from follicular cells into the cytoplasm keeping the intracellular iodine concentration always higher than in the extracellular fluid [6].
Once iodine uptake ion occurs, the $I^-$ captured by the follicular cell migrates to the apical surface, where it is oxidized and converted to its active form ($I^+$) by the enzyme thyroid peroxidase [7, 8]. The thyroid peroxidase enzyme is responsible for catalyzing the incorporation of $I^+$ to tyrosine residues and the binding of iodotyrosine molecules (already incorporated) in thyroglobulin (phenomenon known as organification) [9]. The now iodinated tyrosine molecules are grouped forming the molecules of thyroid hormones [5, 6] One diiodotyrosine added to one monoiodotyrosine results in 3,5,3 triiodothyronine (T3); whilst two diiodotyrosine will form thyroxine (T4) [9]. The hormone triiodothyronine (T3) is less abundant, but it has a much higher biological activity than thyroxine (T4) [10], [11].
Thus, it is clear that iodine is an essential raw material for the synthesis of thyroid hormones. It is taken in food and absorbed into the circulation. The minimum amount of daily consumption is 150 μg/day in adults [12]. However, according to World Health Organization (WHO) and International Council for the Control of Iodine Deficiency Disorders (ICCIDD) guidelines, median urinary iodine values for pregnant women between 150 and 249 μg/L are consistent with optimal iodine intake [12].

## 3. Metabolism of thyroid hormones

After its formation, a part of thyroid hormones is stored and a part is released (by the action of TSH or thyroid stimulating hormone). It is also known that only around 20% of the daily production of T3 is released directly into the circulation by the thyroid gland, since most of the conversion of T4 to T3 occurs in peripheral tissues [10] [11]. This process in which the precursor of (T4) is converted to the active form of the hormone (T3) is known as central and peripheral deiodination, and it is accepted that this process is one of the control pathways of the bioavailability of this hormone [13] [14].
T3 and T4 are deiodinated in the liver, kidneys and other organs [15]. These deiodination reactions works not only to catabolize the hormones, but also to provide local source of T3 [13]. About one-third (1/3) of circulating T4 is converted to T3, 13% of T3 is released into the thyroid and 87% formed by deiodination [13] [15].
The deiodination is performed primarily by two enzymes: the deiodinases 1 and 2 (DIO1 and DIO2) [13] [16]. The DIO1 is

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present in liver, kidney, thyroid, and hypophysis DIO2 is in the hypophysis, brain (is in astrocytes and generates a T3 reservation for neurons; Figure 1) and brown adipose tissue [15] [13]

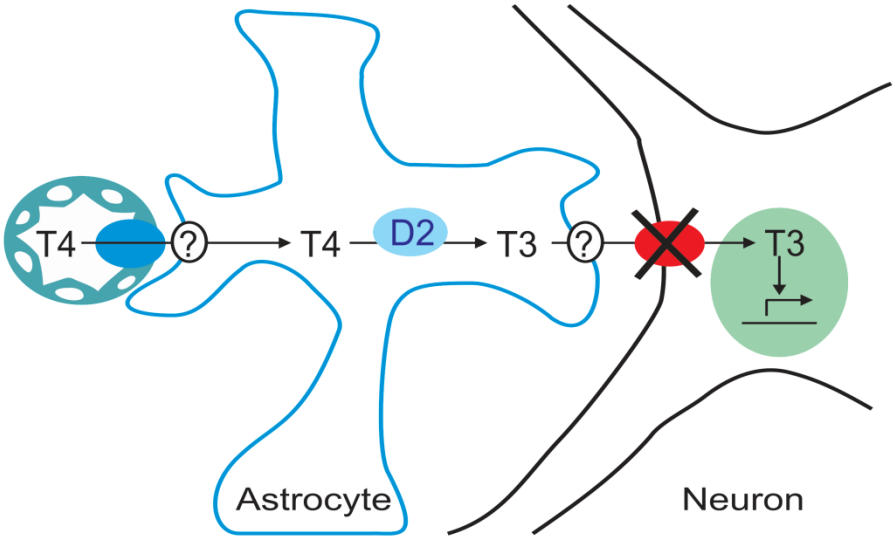



**Fig. 1:** Showing the Conversion of T4 to T3 by the Action of Deiodinase 2 (DIO2).

## 4. Features and functions of T3 and T4 hormones

Thyroid hormones are hydrophobic molecules, liposoluble and therefore cross the cell membrane of most cells where they will perform their biological roles. Among its functions include the elevation of mitochondrial ATP synthesis [17], as well as having effects on body weight and fat metabolism [2]. Other non-genomic functions of thyroid hormones include modulation of intracellular levels of $Na^+$, $Ca^{2+}$, $K^+$, glucose transport, the activation of PKC (protein kinase C), PKA (protein kinase A), ERK / MAPK (kinase regulated by extracellular signals and mitogen-activated protein kinase, respectively) and the regulation of phospholipid metabolism by the activation of phospholipase C and phospholipase D [18]. Therefore, its functions are associated with increased consumption of oxygen in the cells, growth and development of mammals, lipidic metabolism, enhance absorption of carbohydrates and regulate thermogenesis [2].

## 5. Mechanisms of action

The receptors for thyroid hormones vary in quantity and expression in different types of tissues [19].
In general, thyroid hormones bind to intracellular receptors, which will bind to the DNA sequences called responsive elements to thyroid hormones forming preferentially heterodimers [20]. The mRNA of receptors for thyroid hormone (TR) was detected during the development by the eleventh and fifteenth embryonic day (E11-E15) in the CNS of rats and its protein was detected in different brain regions of rats in the fourteenth embryonic day - E14 [21].
The family receptors for thyroid hormone (TR) consists of two isoforms: α receptors for thyroid hormones (TRα) and β receptors for thyroid hormones (TRβ) [22]. The TRα receptors are still divided into TRα1, TRα2 and TRα3. The three isoforms differ in their carboxyterminal portion, only TRα1 bounds to T3 [23]. Two other variants of TRα, TRΔα1 and TRΔα2 that have been identified appear not to bind to T3 nor DNA, proving to be inhibitors of TR [24].
The second group of receptors, TRβ, include the TRβ1 TRβ2, TRβ3 TRΔβ3 variants [22]. These three proteins demonstrated to play different roles among themselves. In fact, we can consider receptors for thyroid hormones in the literal sense of the word, only the isoforms of TRα1, TRβ1 and TRβ2, for binding to T3 and activating or inhibiting gene transcription [25].

Studies using TRα1 and TRβ receptors with mutations that removed their ability to connect to T3 suggest an important role of non-activated TRs, explaining, at least in part, this discrepancy phenomena [26]. These facts also support the hypothesis of the importance of non-genomic actions of thyroid hormones (such as actin polymerization, neurite outgrowth and synaptic efficacy).
Thyroid hormones play also a key role during the critical period, relating to axonal outgrowth, synapse formation, myelination, proliferation and neuronal migration [25].

## 6. T3 and T4 effects in nervous system development

The appearance of the thyroid in rats occurs approximately at the ninth embryonic day (E9) [27]. In this step, the gland already concentrates thyroglobulin and is able to perform the uptake of iodine. Basically, hormone embryo source is maternal. The detection of the hormone in mouse embryo happens already in the ninth embryonic day (E9), with different levels of T3 and T4, being T3 the most abundant [27]. Experimental reports have demonstrated that the mouse trophoblasts had a concentration of 21% of the maternal concentration of T4 and 54% of T3 [28], as well as experiments demonstrated that even small deficiencies of maternal iodine are able to reduce the T4 levels of the fetus [29], showing that normal maternal serum levels of T4 are critical to maintaining adequate levels of this hormone in the embryo a suitable local conversion to T3. The total levels of T3 and T4 increased significantly from E18 to birth by the maturation of the thyroid gland. After birth, the plasma levels of T4 rises sharply to a peak in the seventeenth postnatal day (DPN17) [30], followed by an elevation in parallel, T3 levels which will reach its peak in DPN28. The total T3 levels that are standard in adult rats are achieved in DPN40 [27].
Thyroid hormones are essential for brain development [31]. The early development of neural tube, by the eighth embryonic day (E8), coincides with the beginning of development of thyroid and, somehow, with the emergence of receptors for thyroid hormones [27]. During the same period, neurogenesis in the central nervous system starts (from E10) [31].
Various phenomena of development (and adulthood) are influenced by thyroid hormones, such as axonal and neuritic growth, synaptogenesis, neuronal survival and migration, myelination and synaptic efficacy [32]. In cerebellar ontogenesis, for example, experiments have shown that thyroid hormones act by mediating epidermal growth factor (EGF), providing an increase of neurite numbers in astrocytes [33]. The regulation of neurotransmitter release in the hippocampus was also influenced by the presence of

thyroid hormones; electrophysiological studies of short-term synaptic plasticity showed that facilitation of paired pulse patterns were found to be extremely modified in animals with hypothyroidism, this condition being reversible with the administration of thyroid hormones [34].
Investigations on cell proliferation in the sub-ventricular zone (SVZ) of the hippocampus also demonstrated that T3 and its receptor alpha (TRα) play an important role in neurogenesis in this region [35]. Effects on extracellular matrix synthesis were also observed in cerebellum, since the absence of thyroid hormones delay laminin expression [36] [37], and their levels were 35% lower than control animals (Farwell et al., 1995).
In the cerebellum, several anatomical alterations induced by perinatal hypothyroidism have been documented, as follow: reduction of growth and branching of dendritic arborization of Purkinje cells [39] [40] [41] [42]; decrease of synaptogenesis between Purkinje cells and granule cell axons [42] [43]; delayed proliferation and migration of granule cells [44]; delayed myelination [45]; and changes in synaptic connection among cerebellar neurons and afferent neuronal fibers [46] [47] (Figure 2).

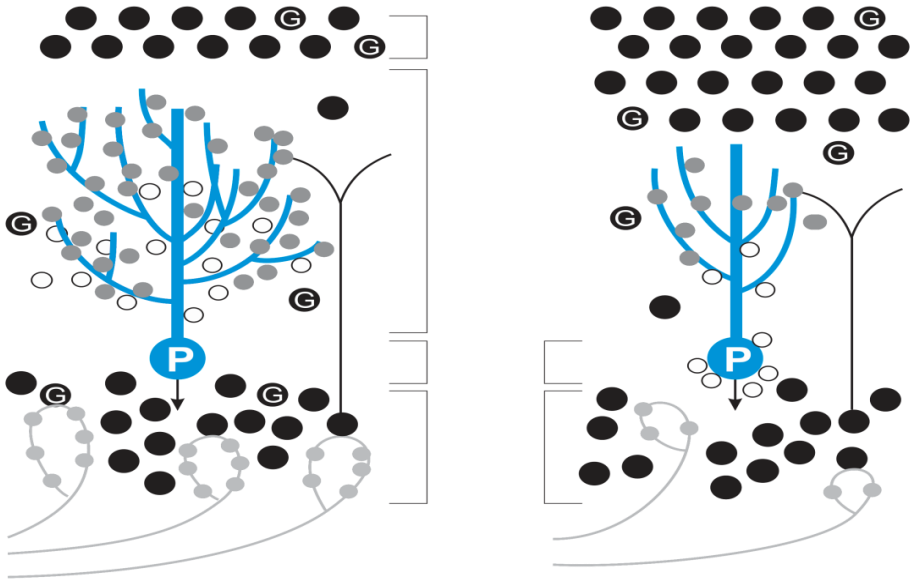



**Fig. 2:** Schematic Images Show the Layers of the Cerebellar Cortex Cells; on the Left, the Layers of A Euthyroid Individual (Normal Levels of Thyroid Hormones) Cells with Extensive Branching (Especially Purkinje Cells, "P" - Blue) Forming Extensive Number of Synapses; and on the Right, the Cell Layout of A Cerebellar Cortex of an Individual with Reduced Levels of Thyroid Hormones, Showing Low Branching Cells (Including Purkinje Cells - Blue) and Reduced Number of Synapses.

## 7. Effects of inadequate dietary intake of iodine to the nervous system

Congenital hypothyroidism is the most common and treatable cause of mental retardation and its prevalence in this context is about 1/3000 births [48]. Congenital hypothyroidism is a major cause of mental retardation in humans, and effects related to hypothyroidism (deficiency of thyroid hormones) congenital vary with the intensity of disability [49]. The cretinism is the most severe picture related to congenital hypothyroidism and includes symptoms such as spasticity, severe mental retardation and deafness [50]. Poor motor coordination effects, ataxias, spastic diplegia, muscular hypotonia, strabismus and learning disorders also are related to congenital hypothyroidism [48]. Frameworks of depression and memory disorders are also present in adults [51].
Despite knowing these aspects, little is known about the cellular, molecular mechanisms and pathways by which thyroid hormones act in regulating the nervous system. There are still several issues related to the phenomena involved in these processes. The accurate determination of the cause of the disturbances found so far, are derived directly from the maternal hormonal deficit [52], secondary to metabolic disorders of the fetus or both.

## 8. Conclusion

Therefore, it is clear that the normal development of the nervous system requires adequate amounts of T4 throughout the development. Initially it is provided by the mother and then the maternal and fetal thyroid. We can conclude that sufficient T4 production by maternal and fetal thyroid requires increase in the dietary intake of iodine [19] [50], and supplements containing potassium iodide (KI) is strongly recommended.

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