Review Article

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Impact of thyroid hormones on brain development

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A B S T R A C T

Thyroid hormones (THs) including triiodothyronine (T3) and tetraiodothyronine (T4) perform an essential role in brain development. The active form (T3) of THs is produced after metabolism and transported in different areas of the brain. This active form interacts with different types of glial cells and stimulates the expression of various genes to produce typical growth proteins. These proteins control many brain developmental processes such as synaptogenesis, neurogenesis, cell proliferation, differentiation, migration, and maturation. The early brain development is dependent upon THs coming from the maternal origin, therefore, during pregnancy, the inadequate intake of iodine (I2) by pregnant mothers is associated with various clinical manifestations. The reduction in THs levels can alter these specific brain developmental processes, thereby changing the cognitive performance, however, THs supplementation can recover the normal circumstances.

Key words: Thyroid hormones (THs), Deiodinases, Thyroid receptors (TRs), Glial cells, Brain developmental processes.

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Introduction

Thyroid gland (TG) produces T_4 and T_3 which are considered as important regulatory compounds. These compounds play a vital role in the development of brain functions .[1] THs produce their specific actions by binding with thyroid receptors (TRs).[2] The active form (T_3) is generated by the deiodination of T_4 and a variety of transporters are available that control the transport of THs.[3] The small amounts of theses hormones are also derived from maternal origin during early gestation period when fetal thyroid axis is not fully developed.[4] The deficiency of THs alters many developmental processes in the brain such as myelination, differentiation, and migration of neuronal cells,[5] synaptogenesis and plasticity (Bernal, 2007).[6] The low concentration of THs produces severe and permanent structural alterations in the nervous system by disrupting these neuronal developmental processes, however, THs replacement therapy can recover the normal situation. [7]

The purpose of this study is to expose the impact of THs on brain development to entire health sectors of those particular countries of the world where there is no particular attention is given on this fact such as in Pakistan. Due to disruption in thyroid status, many cases of brain dysfunction arise but the reality is ignored due to the lack of consideration about this aspect. Therefore, in this review study, a number of facts and figures have been mentioned which will led us towards an important proposal that THs may effect brain development by regulating various neuronal processes and we have also provided context for this purpose.

Metabolism of thyroid hormones

There are three types of proteins that participate in the deiodination of THs including deiodinase-1 (Dio-1), deiodinase-2 (Dio-2) and deiodinase-3 (Dio-3). The Dio-1 possesses high sensitivity towards T_3).[8] It causes deiodination of both the inner and the outer rings.[9] Similarly, Dio-2 is capable of catalyzing the deiodination of Outer-ring and it has affinity for thyroxine (T_4). The Dio-3 causes the deiodination of inner-ring. It prevents the high levels of serum THs coming from maternal origin.[10] The Dio-2 synthesizes T_3 by catalyzing the

deiodination within CNS and it is concentrated within astrocyte cells (Horn and Heuer, 2010).[11] The Dio-3 is represented as another significant factor that regulates the conversion of T_3 to T_2).[12]

Thyroid hormone receptors and isoforms

The nuclear receptor proteins including thyroid receptor alpha (TRα) and thyroid receptor beta (TRβ) are expressed by TRα and TRβ genes respectively (Kester *et al*., 2004; Bernal, 2002).[13,14] The TRα covers about 70 to 80 percent of TR expression (Williams, 2008) and it is located at 17th chromosome. The TRβ is located at 3rd chromosome. (Bernal, 2002; Harvey and Williams, 2002).[14,15] There are two isoforms that are generated from TRα gene designated as $TR\alpha_1$ and $TR\alpha_2$. $TR\alpha_2$ is a combination of two isoforms which are termed as receptor variants (Bernal, 2002).[14] The TRβ gene is also transcribed as thyroid receptor β_1 and β_2. Similarly, the two more TRs are produced from TRβ gene in rats including thyroid receptors β_3 and $_{dal}\beta_3$. The $TR_{dal}\beta_3$ is produced as a truncated protein which does not contain any DNA-binding domain and N-terminal. On the other hand, thyroid receptors β_1, β_2 and β_3 are entirely functional receptors (Harvey and Williams, 2002). [15]

Conversion and transportation of thyroid hormones

The transfer of THs from one place to another is mostly carried out by transthyretin protein.[16,7] This protein is produced in remarkable quantities from choroid plexus.[16] There are some other transporters that regulate the transport of T_4 and T_3 across the cell membrane. These transporters include sodium/taurocholate cotransport ing polypeptide (NTCP), mono-carboxylate transporter (MCT), organic-anion transporting polypeptide (OATP) and heterodimeric amino-acid transporter (HAT). However, MCT_8, $OATP_{1C1}$, MCT_{10} and L-type amino-acid transporter (LAT_1) are widely expressed in the brain.[17] The blood circulation will transfer T_4 to brain where it is shifted into astrocytes via $OATP_{1C1}$ transporter. Here, the T_4 is converted into T_3 with the help of Dio-2 and after conversion, T_3 moves outside via specific cell membrane transporter and again takes up by the neurons via McT_8 as shown in figure 1 [16]

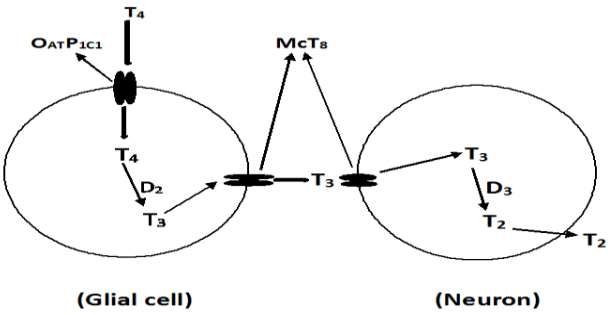

Figure. 1: The conversion of THs and their uptake by different types of cells with the help of membrane transporters. Where OATP1c1: (organic anion transporting polypeptide), McT8: (monocarboxylate 8 transporter), D2: (deiodinase-2), D3: (deiodinase-3), T2: (diiodothyronine). (Self-made Figure)

Role of maternal thyroid hormones

The maternal THs exert a direct impact on the brain during pregnancy.[18,19] In the past it was considered that the placenta is impermeable to THs. Therefore, it was hypothesized that THs might not be necessary for fetus brain development. Now It is cleared that the human and rats contain T_4 and T_3 during the embryonic stages which truly come from the maternal side as shown in figure 2. The transfer of THs from mother takes place till birth of fetus then after the onset of fetal TG, the transfer of maternal THs is no more necessary. When there is impedance in fetal thyroid functioning, THs start to transfer across the placenta from the matriarch to fetus.[4] In fetus THs are present usually on 18th embryonic day[18,19] and the early neural migration and proliferation is based on thyroxine coming from the maternal side during 1st trimester of the gestation period. One thing of great concern is that the level of T_4 in fetal fluid is higher as compared to mothers. This difference is associated with certain types of proteins such as transthyretin (TTR) which bind with T_4 and the level of T_4 coming from maternal side.[20]

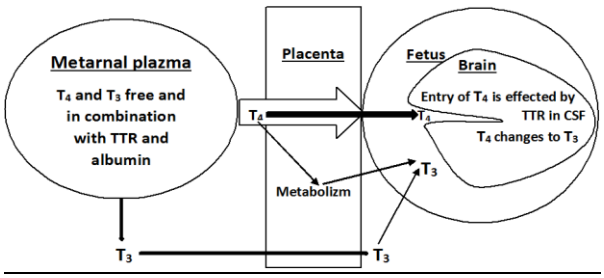

Figure. 2: The source of THs for newly developed fetus before the onset of thyroid gland. Where TTR: (transthyretin receptor), CSF: (cerebrospinal fluid). (self-made figure)

Thyroid hormones and migration of neuronal cells

The inadequacy of THs can affect the astrocyte cells which will ultimately disturb the migration of neuronal cells. The astrocytes release laminin, a protein that is responsible for neuronal cell migration. It acts as a guidance moiety. The inadequacy of THs in rat cerebellum slows down the gene expression of laminin protein.[21,22] This inadequacy is also associated with modulation of actin filaments which will ultimately disrupt the formation of focal contacts on astrocyte's surface while T_4 treatment again reorganizes these contacts.[22]

Thyroid hormones and synaptogenesis

The synapse formation is reduced in the cerebellum due to low levels of THs. It is supposed that THs act directly to regulate the process of synaptogenesis.[7] These hormones have a strong influence on intraneuronal networks. For example, a reduction in the number of synapses, between the mossy fibers and the hippocampal pyramidal cells of CA-3 niche, occurs due to low levels of THs.[7] The overall density of synapses was decreased in the hypothyroid nervous system because the dendritic, as well as the axonal outgrowth, had been disrupted. However, some past studies did not indicate any reduction in pyramidal cells in CA-3 niche.[23] But other studies have revealed a reduction in pyramidal cells in CA-3 niche.[24] Some other researches have also exhibited that THs influenced the degree of excitation in hippocampal CA-3 and CA-1 niches.[23] The hippocampus is that part of the brain which is required for the learning process as well as for memorization and this region is highly sensitized to THs.[18, 25] Therefore, low serum levels of THs can induce behavioral defects.[18]

Thyroid hormones and cell proliferation

The THs play a remarkable role in the proliferation of oligodendrocyte precursor-cells (OPCs). These cells are usually known as oligodendrocyte type-2 astrocytes (O-2A) cells. When THs are not available then O-2A may proliferate for an unspecified period. But in the presence of THs these precursor cells can proliferate up to 8 cell-divisions. After this the division of cells is ceased and they are differentiated into fully mature oligodendrocytes.[26,27] THs withdraw the OPCs from the cell cycle and stimulate the terminal differentiation at a particular time. Hence, these hormones keep the duration of proliferation within a normal limit.[27] Similarly, the balance between various TR-isoforms can also stimulate the hormonal sensitivities. In this prospective the studies have indicated that TRα arrests cell cycle during proliferation of cells.[27,28]

Thyroid hormones and myelination

The expression of myelin associated glycoproteins such as myelin basic proteins (MBPs), known as the basic constituents of the myelin sheath, have been reduced in neonatal hypothyroidism[29] because THs regulate the synthesis of these specific basic proteins thus affecting both the number as well as the contents of myelinated axons.[26] So, THs may regulate the process of myelination either by enhancing the differentiation of glial cells such as oligodendrocytes or by stimulating the production of myelin associated components. Furthermore, THs also catalyze the mixing of these components in order to form a complicated myelin sheath.[30] The neurodevelopment disruptions have been observed in many areas of the brain due to a reduction in proper myelination. However, thyroid supplementation can reverse all of these effects if it is given before fourteen-days during extrauterine life (Chan and Kilby, 2000).[31] In contrast, the adult myelin disruptions remain permanent throughout life and THs supplementation cannot recover the normal situation.[12] In the absence of THs the progenitors of oligodendrocytes known as O-2A cells proliferate for an indefinite period but THs administration can stop the proliferation of O-2A cells and bring about terminal differentiation.[32] Hence, it is proven that the hypothyroidism slows down the process of myelination and alters the thickness of the myelin sheath. [33,34]

Thyroid hormones and neurogenesis

The neurogenesis in brain is limited to only two particular areas; one of them is hippocampal dentate gyrus and the other area is known as subventricular-zone (SVZ).[12] The hypothyroidism can alter the production of neurons in these particular areas by lowering the survival of progenitors but did not disturb the proliferation state.[35] But later on, it was demonstrated that the hypothyroidism also decreases the neuroblast count in the subgranular zone (SGZ) of the dentate gyrus as a result of which neurogenesis is reduced in this particular niche. In contrast, the administration of THs accelerates the process of neurogenesis especially in these particular portions.[36] The administration of T_3 enhances the differentiation of neuronal stem cells (NSCs) to neuroblasts).[12] These NSCs are derived from neuroepithelium that produces many cells in the brain

including astrocytes, neurons and oligodendrocytes[37] Hence, T_3 could adjust homeostasis of adult SVZ particularly by instigating the gene repression that is involved in NSCs replication and also suppressed various regulators that could induce the progression of cell cycle, for example, avian myelocytomatosis virus oncogene cellular homolog (c-Myc) and cyclin-D1. [36]

Thyroid hormones and neuronal cell differentiation

The cell differentiation is associated with respective growth proteins whose expression, on the other hand, is dependent upon THs. Therefore, any fluctuation in THs can disturb the normal process of cell differentiation.[38] The hypothyroid rats usually exhibited low levels of growth proteins such as brain-derived-neurotrophic-factor (BDNF), nerve-growth-factor (NGF) and neurotrophin-3 (NT_3). The brain developmental defects are produced in neonates when the expression of BDNF is reduced in specific brain niches as a result of low levels of THs. [25] The THs also regulate the expression of NT_3 thus it may regulate the development of.[24] The low levels of serum THs also disturb many cells in other areas of the brain such as in the cerebral cortex by retarding cell differentiation in IML, consequently, few basket cells are produced.[41] In contrast high levels of serum THs stop the premature migration and differentiation of cells.[38] Up till now the exact mechanism is not known. The experimental studies have also revealed that there are a number of other modulators participating in this behalf, for example, cyclin-D_1, E_2F_1, usually known as the modulators of cell cycle, and p_{27}. The cell cycle modulators control phase transition i.e from G_1 to S phase. Other candidates are cyclin-dependent kinase inhibitor (p_{27}) and the level of p_{27} was upregulated by T_3. The down regulation of cyclin-D_1 and E_2F_1 protein and up regulation of p_{27} kinase inhibitors mof-GFA_{ay} will lead the cells towards differentiation.[39]

Thyroid hormones and maturation of neuronal cells

The inadequacy of THs in rats decrease the overall count of matured astrocytes and oligodendrocytes in brain.[26] This is believed to be happened due to the low glial-fibrillary acidic protein (GFAP) and F-actin contents in basal-forebrain and hippocampus. it has been confirmed from the cell cultures that T_3 upregulates the production of GFAP filaments and converts the polygonal flat astrocyte into mature cells.[7] Mazano et al have also demonstrated the influence of THs on the maturation of cells in the brain because THs modulate the astrocyte count in-Vivo. Side by side, in the rat cerebellum, THs also control the maturation of some other cells such as Golgi-epithelial cells.[40] So, any disturbance in the levels of THs can adversely effect the maturation of cells in the brain.

Table I: This is showing the impact of low THs on brain developmental processes. Where (↓) = Decrease

Brain developmental processes	Impact of low THs
Migration	Migration of neuronal ↓
Synaptogenesis	Synapse formation ↓
Neurotransmitter release	Secretion of neurotransmitter ↓
Myelination	Synthesis of myelin ↓
Neuronal outgrowth	Outgrowth ↓
Arborization	Purkinje cell arborization ↓
Proliferation	Division of cells become out of normal limit.
Neurogenesis	Production of neuronal progenitors ↓
Differentiation	Cell differentiation become out of control
Behaviors	Induce defects in behaviors

Conclusion

The developmental impact of THs on the brain can be revealed by identifying organizational deficits at the cellular level. During the clarification of molecular basis, several genes have been recognized which are regulated by THs and produce specific growth factors or typical proteins which regulate brain developmental processes. So, there is an existence of consistency between theses genes and brain developmental processes. As these genes are regulated by T_4 and T_3 so it is concluded that any defect in status of THs can disturb the development of brain which may lead to serious behavioral complications. Sometime, THs also interact directly with glial cells to control brain development. In this regard the levels of maternal THs have also equal potential because early brain development is totally dependent upon THs coming from mother side. By various experimental studies it has been proved that the low levels of THs can disturb the brain development while thyroid hormone's supplementation can recover or improve the situation when it is given at specific period.

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