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Thyroid hormones: possible roles in epilepsy pathology

Seyedeh Masoumeh Seyedhoseini Tamijani¹, Benyamin Karimi², Elham Amini², Mojtaba Golpich², Leila Dargahi³, Raymond Azman Ali², Norlinah Mohamed Ibrahim², Zahurin Mohamed⁴, Rasoul Ghasemi⁵, Abolhassan Ahmadiani*¹,⁴

¹Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
²Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Cheras, Kuala Lumpur, Malaysia
³NeuroBiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
⁴Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia
⁵Neurophysiology Research Center and Department of Physiology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Seyedeh Masoumeh Seyedhoseini Tamijani, Benyamin Karimi and Elham Amini contributed equally to this work and should be considered as co-first authors.

*Corresponding authors: Abolhassan Ahmadiani; Email: aahmadiani@yahoo.com & Rasoul Ghasemi; Email: ghasemii6@sbmu.ac.ir

Abstract

Thyroid hormones (THs) L-thyroxine and L-triodothyronine, primarily known as metabolism regulators, are tyrosine-derived hormones produced by the thyroid gland. They play an essential role in normal central nervous system development and physiological function. By binding to nuclear receptors and modulating gene expression, THs influence neuronal migration, differentiation, myelination, synaptogenesis and neurogenesis in developing and adult brains. Any uncorrected THs supply deficiency in early life may result in irreversible neurological and motor deficits. The development and function of GABAergic neurons as well as glutamatergic transmission are also affected by THs. Though the underlying molecular mechanisms still remain unknown, the effects of THs on inhibitory and excitatory neurons may affect brain seizure activity. The enduring predisposition of the brain to generate epileptic seizures leads to a complex chronic brain disorder known as epilepsy. Pathologically, epilepsy may be accompanied by mitochondrial dysfunction, oxidative stress and eventually dysregulation of excitatory glutamatergic and inhibitory GABAergic neurotransmission. Based on the latest evidence on the association between THs and epilepsy, we hypothesize that THs abnormalities may contribute to the pathogenesis of epilepsy. We also review gender differences and the presumed underlying mechanisms through which TH abnormalities may affect epilepsyhere.

Keywords: Seizures, Temporal lobe epilepsy (TLE), Hyperthyroidism, Hypothyroidism, Brain development, epileptogenesis.
1. Introduction

The thyroid hormones (THs), triiodothyronine (T3) and its prohormone thyroxine (T4) are important regulators of gene expression. Through interaction with thyroid hormone receptors (TRs), THs regulate cell development, homeostasis, differentiation, growth and metabolism [1]. Thyroid hormones act in the brain where they play an essential role in fetal and post-natal brain development as well as the maintenance of adult brain function [2]. The importance of THs in the central nervous system (CNS) function is well confirmed in both neonatal and adult hypothyroidism [reviewed in [3]]. In addition, THs promote CNS repair, as it has been demonstrated that CNS re-myelination is dependent on these hormones [4]. In addition, THs have non-genomic and genomic effects on mitochondrial biogenesis and function [5] and decreased activity of THs in humans is linked to impaired mitochondrial biogenesis and function [6]. Furthermore, THs abnormalities including both hypothyroidism and hyperthyroidism, have been shown to induce the production of reactive oxygen species (ROS) and affect the oxidative capacity of the adult brain by modulating antioxidant enzymes [7]. THs also specifically modulate the development and function of GABAergic interneurons in vitro and in vivo [8, 9].

Epilepsy is one of the most common chronic neurological disorders affecting people of all ages [10]. It is a disorder of recurrent and spontaneous seizures resulting clinically into permanent alterations of normal function and morphology of neuronal cells and even cell death [11, 12]. Though the actual pathogenesis of epilepsy remains unclear, accumulating evidence indicates that mitochondrial dysfunction [13], oxidative stress [11] and failure in the regulation of excitatory (glutamate) and inhibitory (GABA) amino acids in the brain [14], are among important factors modulating its pathogenesis and seizure generation.

Knowing that mitochondrial dysfunction, oxidative stress and GABAergic deregulation are among the main characteristic of epilepsy and the fact that these abnormalities are associated with THs deficits, all strengthen the viewpoint that THs might affect epilepsy pathogenesis. The present review therefore provides an overview of recent developments in the field of THs function and its possible role in the pathogenesis of epilepsy, as a chronic neurological disorder.

2. Thyroid hormones

The thyroid hormones, T3 and T4, are two tyrosine-based hormones that are synthesized by the thyroid gland. The release of TH is controlled by the hypothalamic–pituitary–thyroid axis (HPTA). The hypothalamus releases thyrotropin-releasing hormone (TRH) which stimulates the
pituitary gland to release thyroid stimulating hormone (TSH). TSH binds to its receptor on the thyroid gland and activates the synthesis and release of THs. The majority of THs released by the thyroid gland is T4 which is then enzymatically deiodinated to a more potent form, T3[15]. Although, THs exert some non-genomic effects by binding to a number of intracellular targets, as well as membrane receptor on integrin αVβ3[16], these hormones mediate their main biological functions primarily at the genomic level. The genomic effects of THs are mediated by a subgroup of the nuclear hormone receptor (NR) family of the ligand activated transcription factors. In order to interact with TRs, THs must enter the cellular nucleus and bind to TRs that are already bound to regulatory regions of the target genes. To our knowledge, two major isoforms of TRs namely TRα and TRβ, have been characterized which are encoded by separate genes (on human chromosomes 17 and 3). Alternative splicing of these genes, gives rise to additional heterogeneity for each member of the TRs (TRα-1 and c-erbAa-2 and TRβ-1 and TRβ-2) [reviewed in [17]]. In contrast to the nuclear effects, the extra nuclear effects, not dependent on nuclear receptors could occur within a short period of time and may be facilitated by signal-transducing pathways such as protein kinases and cyclic adenosine monophosphate (cAMP) [18, 19].

2.1. Thyroid hormone in CNS

As previously mentioned, CNS is one of target tissues for THs where these hormones play an essential role in prenatal and postnatal brain development as well as the maintenance of its physiological function. Generally, the concentration of THs in the CNS is much less than in the serum. This difference is caused by the difficulty of transporting THs across the blood brain barrier (BBB). Two main pathways have been proposed by which THs crosses the BBB into the CNS. In the first pathway, THs crosses the BBB through OAT1P1C transporters and enter astrocytes end feet where T4 is converted to T3, via the enzyme deiodinase 2. In the second pathway, MCT8 transporters help THs to enter the CNS. THs can also directly enter the brain via gaps in the BBB, where the astrocytes end feet do not completely cover the capillaries [reviewed in [3]]. Like the periphery, the central effects of THs are primarily triggered by binding to TRs and then repressing or activating the target genes[20].
2.2. Functions of thyroid hormones in CNS
The biological functions of T4 and T3 in the CNS have been widely reported. Some reports show that T4 exerts only nongenomic effects in the brain while T3 serves as a unique agonist for nuclear TRs. However, others show that TR-α1 acts as a sensor for both T3 and T4 while TR-β1 is more responsive to T3. Therefore, it seems that the transcription response mediated primarily by TR-α1 might be triggered by both T3 and T4 and more pure T3 effects are mediated by TR-β1[3].

One of the best-known functions of THs in the CNS is their role in CNS development. It has been shown that gestational/neonatal hypothyroidism changes cell migration pattern and decreases cell number, synaptogenesis and dendritic arborization, as well as axonal myelination. These developmental defects induced by severe THs depletion are demonstrated in the cerebellum, neocortex and hippocampus, and in heavily myelinated white matter tracts, such as the corpus callosum[21]. It has been consistently shown that THs deficiency during brain development (congenital hypothyroidism) can lead to irreversible and progressive intellectual deterioration (cretinism) and neurological deficits. Most of these defects could be prevented by timely diagnosis and THs replacement therapy[22, 23]. In addition to the early stages of life, appropriate THs signaling also plays an essential role in adult brain functions. The importance of THs in the function of adult brain is well demonstrated in adult hypothyroidism which affects the hippocampus and cortex and results in mood and behavior abnormalities like anxiety, and depression-like symptoms, as well as memory impairment [24, 25]. Adult-onset hypothyroidism reduces the number of newborn neuroblasts in the dentate gyrus. THs deficiency impairs adult neurogenesis, particularly in the hippocampus, reduces hippocampus volume and contributes to cognitive problems in hypothyroidism[25, 26]. In addition, it has been revealed that hypothyroidism is also associated with other complications such as impaired myelination, delayed development of the dendritic tree, reduced glial cells and axo-dendritic synapses[27, 28].

3. Epilepsy and its pathological features
The most characteristic feature of epilepsy is a continuous rise in neuronal excitability which leads to an unduly sustained and synchronous discharge of a group of neurons. In about half of epileptic patients, no causative factors have been found yet while in the other half, different causative factors such as oxygen deprivation, trauma, infection, tumors and metabolic imbalances are suggested to be involved in abnormal cellular discharges [29]. Malfunctions of cerebral cortex development also participate in the pathogenesis of epilepsy [30]. It has consistently been proposed that macro or
microscopic cortical abnormalities that may occur in the first or second trimester of pregnancy could lead to epileptic seizures [31]. Non-neuronal cells of the CNS such as microglia and astrocytes play a pivotal role in the maintenance of tissue homeostasis and neuronal activity. Therefore, it is believed that dysfunction of these cells may also participate in the pathogenesis of epilepsy[32].

Considering the essential role of THs in early foetal brain development and the profound effects of THs abnormalities on brainneuronal cytoarchitecture, neurotransmitters and pro/antioxidant systems[33], it would be conceivable to hypothesize that THs dysregulation might play a determining role in the pathogenesis of epilepsy. In the other sections of this review, THs and their dysregulation, as well as how they may participate in the pathophysiology of epilepsy, have been discussed.

4. Thyroid hormones, adult CNS and epilepsy

Head injury is one of the causative factors of adult epilepsy, and on the other hand, patients with brain injuries have been shown to have lower levels of THs. In patients with traumatic brain injury (TBI), THs metabolism is defected, and conversion of T4 to the active form T3 catalyzed by deiodinase enzyme becomes impaired. Furthermore, in the early phases of brain injury, TSH level is decreased and this might be another causative factor for THs decreased levels [reviewed in [34]]. In this regard, Crupi et al. investigated the effect of T3 on a murine model of TBI and reported that treatment of mice with T3 (1.2μg/100g body weight, i.p) one hour after TBI can significantly protect against brain trauma and improve motor and cognitive function [35]. Though the repair capabilities of the spinal cord and brain are limited, THs exert regenerative effects on nerves cells. The myelination process was also shown to be dependent on THs function in both peripheral and central nervous systems [4]. THs are able to induce oligodendrocytes formation from multipotent neural stem cells and also play a role in regulating different developmental stages of oligodendrocytes [36, 37]. However, the potential protective effects of THs in post-TBI seizure events still remain unknown.

In addition, it has been shown that thyroid deficiency during pregnancy and lactation make offsprings more susceptible to audiogenic convulsion [38]. Persistently, it has also been reported that mice lacking TRβ are more susceptible to audiogenic seizures [39]. Among the genes affected by THs, neurotrophic factors are of special significance, as they play a key role in pathophysiological conditions such as seizures [40]. Neurotrophic factors exert a variety of effects on neural differentiation, survival and growth, and also influence neurotransmitter synthesis, synaptic plasticity
and neural excitability [41]. Neurotrophic factors that are shown to influence epileptic conditions and seizures include fibroblast growth factor-2 (FGF-2), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), nerve growth factor (NGF), glial cell line derived neurotrophic factor (GDNF), and the vascular endothelial growth factor (VEGF) [42]. While some studies imply that increased expression of many neurotrophic factors after brain injury or acute seizures contribute to the neuroprotection of the injured brain [43], some others proposed that some of these neurotrophic factors such as BDNF and NGF, actually promote epileptogenic changes [44]. It is well known that epileptogenic insults increase the synthesis of BDNF and activation of trkB receptors [45]. Subsequently, studies in animal models of epilepsy show an increase of BDNF levels in surviving hippocampal cells after glutamate receptor activation, at early post seizure delay [46, 47]. Though the precise role of neurotropic factors in post seizure phase is not well defined, the potential protective effects of THs through modulation of neurotrophic factors or other genes expression on seizure-induced neural damage needs to be studied.

5. Thyroid hormones and pathogenesis of epilepsy / epileptogenesis

5.1. Thyroid hormones and mitochondria
Several lines of evidence showing that oxidative stress, free radicals and mitochondrial dysfunction play important roles in seizure generation and epileptogenesis are available [13, 48, 49]. On the other hand, THs have non-genomic and genomic effects on mitochondrial biogenesis and function [5]. Accordingly, THs are shown to regulate the expression of target genes and eventually mitochondrial biogenesis through three different pathways (Figure 1). In the first pathway, T3 directly affects the mitochondria through the binding of a mitochondrial localized receptor [50]. A truncated product of the TRα gene named P43, located inside the mitochondria provides binding sites for T3 in the mitochondrial inner membrane. P43 attaches to numerous thyroid hormone response element (TRE)-like sequences on the mitochondrial genome and triggers transcription in a ligand-dependent way in the presence of TH [51]. Consequently, it has been reported that the over-expression of P43 in vivo and in cell culture contexts increases protein synthesis and mitochondrial transcription [51]. In the second pathway, T3 attaches to nuclear-localized TRs and TREs to control gene expression of nuclear-encoded proteins that are destined to the mitochondria and in this way affect mitochondrial biogenesis [50]. In the third pathway, intermediary factors such as the peroxisome proliferator-activated receptor gamma (PPARγ), nuclear respiratory factor 1 (NRF-1), NRF-2 transcription
factors, as well as the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and peroxisome proliferator-activated receptor gamma, coactivator 1 beta (PGC-1β) may be generated by THs and then these co-activators enter the mitochondrion where they could regulate another group of THs target genes[52]. Therefore, it seems that T3 can regulate mitochondrial gene transcription either via a direct pathway through THs receptor actions or via an indirect pathway which includes co-activators and intermediate factors.

![Schematic representation of how THs regulate mitochondrial function](image)

Figure 1: Schematic representation of how THs regulate mitochondrial function (biogenesis, oxygen consumption, and gene expression) affecting nuclear and/or mitochondrion genome. (Direct and indirect pathways).

As earlier mentioned, besides regulation of development and growth, THs acts as a regulator of energy metabolism[53]. T3 strongly increases oxygen consumption and the rate of ATP
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Hydrolysis. Hyperthyroidismis associated with an increased rate of oxygen consumption in most tissues except those from the testis, spleen and adult brain [54, 55]. It is believed that the proton leak through the mitochondrial inner membraneis a key target for THs-induced oxygen consumption. This THs-mediated increase in proton permeability through the inner membrane is thought to be achieved via different mechanisms. Firstly, THs alter the phospholipid composition and fluidity of the mitochondrial membrane [56]. It has been reported that while reduction in rat THs decreases respiratory rates, alpha-glycerophosphate dehydrogenase activity and proton permeability, T3 replacement therapy restores these parameters after 9-12 h [57]. Mitochondrial uncoupling proteins (UCPs) are anion carrier proteins in the mitochondria which dissipate oxidative phosphorylation from ATP synthesis; they are therefore, also referred to as mitochondrial proton leak [58]. Several lines of evidence are available showing that UCPs gene expression is increased by T3 [59-61]. Therefore, T3-induced elevation of UCPs expression is another mechanism by which T3 increases proton leak [62].

In addition, the decreased activity of THs has been shown to be associated with diminished mitochondrial function and biogenesis [6] and interestingly, in cell lines with mitochondrial DNA (mtDNA) deficiencies, THs treatment restores mitochondrial functions [63]. These hormonal effects on mitochondria have been examined in different brain structures and has been reported that mitochondria in the striatum and the cerebral cortex are sensitive to thyroid hormone action [64]. Therefore, it seems that by controlling mitochondrial gene expression, THs modulates mitochondrial biogenesis and oxidative phosphorylation capacity in certain areas of the brain such as the striatum and cerebral cortex [65]. Consistently, it has been evidenced that hypothyroidism during primary mammalian brain development is associated with reduced expression of different mitochondrial genes, as well as mitochondrial impairment. However, the receptor type (nuclear or mitochondrial) and the exact mechanisms by which THs exerts mitochondrial effects during development are still unclear [66].

Compelling proofs obtained from humans and experimental seizure models show that mitochondrial dysfunction and the resulting oxidative stress contributes to the pathogenesis of chronic epilepsy [67, 68]. It has been demonstrated that mitochondrial Complex I in the brain seizure foci decreases in patients suffering from temporal-lobe epilepsy (TLE) [69, 70]. It has also been shown that hippocampal complex I activity decreased in an experimental model of status epilepticus [69]. Impaired mitochondrial metabolism accompanied by deregulated glutamate–glutamine–GABA
cycling was also observed in neurons and astrocytes of epileptogenic hippocampal formations [71, 72]. Collectively, considering the role of THs, particularly T3, in normal mitochondrial functions and the role of mitochondrial dysfunction in epileptic processes, it can be concluded that abnormalities in THs function may participate in the pathogenesis of epilepsy, however, more direct studies are needed to prove this hypothesis.

5.2. Thyroid hormones and oxidative stress

Oxidative stress is an imbalance between the production of oxidant agents and antioxidant activity of defense systems [73]. While the adult brain comprises only about 2% of the entire body mass, it uses 20 to 35% of the total absorbed oxygen in the lung and consumes about 25% of the body's glucose [74]. Mitochondria are the core cell organelle that uses oxygen to produce energy [75]. However, 1-2% of the oxygen used by the mitochondria is incomplete and leads to the production of superoxide radicals in cells. In the presence of free iron and through classical Fenton reaction, superoxide radicals have a high propensity to react with hydrogen peroxide and generate hydroxyl radicals unless these superoxideradicals are deactivated immediately. These hydroxyl and superoxide radicals together with the non-radical oxygen and hydrogen peroxide species are known as reactive oxygen species (ROS), which attack different biomolecules such as proteins, DNA and lipids and mediate the process known as oxidative stress [76].

Previous studies have suggested that ROS might play an essential role in the generation of epileptic seizures [77]. Unlike nuclear DNA which has a histone mediated protection, mtDNA has no such protection. On the other hand, mtDNA is located adjacent to the electron transport chain as the main source of superoxide radical production. Therefore, mtDNA is reportedly considered as an assailable target for oxidative stress [78]. As mammalian mtDNA is the encoding source for some pivotal polypeptides of the oxidative phosphorylation system, any damage to mtDNA might hamper the expression of these important polypeptides and eventually cause mitochondrial oxidative phosphorylation deficiency [79].

It has been shown that THs dysregulation, either hyperthyroidism or hypothyroidism, affects antioxidant/oxidant balance and promote ROS generation [80]. In this regard, Das and Chainy have compared oxidative stress and antioxidant defense parameters of mitochondrial and post-mitochondrial fractions of rat cerebral cortex in hypothyroid, euthyroid, and hyperthyroid states and reported that the body’s thyroid state significantly affects the brain’s antioxidant defense status [7]. While hypothyroidism increases protein carbonyl and lipid peroxidation products as
oxidative stress indices in the mitochondrial fraction of the brain, replacement of T3 restores these parameters[76]. Hyperthyroidism is also associated with increased oxidative stress and affects mitochondria as the primary target of oxidative stress[81].

The brain’s poor antioxidant defense system and high amount of poly-unsaturated fatty acids makes it more susceptible to oxidative attacks compared to other tissues like the lungs and liver[7]. Oxidative stress has been shown to be implicated in a variety of acute conditions like cerebral ischemia and chronic neurological conditions including epilepsy[14]. Evidences abound showing that oxidative impairment of mtDNA and subsequent mitochondrial dysfunction participates in epileptic seizures [13, 82, 83]. Collectively, as both hypothyroidism and hyperthyroidism promote oxidative stress and oxidative stress plays an essential role in the pathogenesis of epilepsy, it would be conceivable to hypothesize that the proper function of THs in the brain might prevent or slow down the development of epileptic seizures.

5.3. Thyroid hormones and GABAergic neurons
Several lines of evidence show that THs modulate the development and function of GABAergic neurons [8, 9]. An in-vitro study on fatal rat brain reports that developmental increase in the activity of glutamic acid decarboxylase (GAD) as the main enzyme in the conversion of glutamic acid to GABA could be increased by T3 administration [84]. Experimental neonatal hypothyroidism has also been shown to decrease the activity of this enzyme in rat brain [85-87]. Beside this enzyme, activities of other enzymes that participate in GABA metabolism such as GABA-transaminase (GABA-T) and succinate semialdehyde dehydrogenase (SSDH) are also affected by THs, and consequently disturbance in THs affects GABA life cycle. While induction of hypothyroidism in developing brain decreases the activity of GABA generating and destroying enzymes, replacement of TH is shown to restore these changes. It has been proposed that impairment in GABAergic inter-neurons development may contribute to locomotor dysfunction and anxiety induced by THs deficits [88-91].

Effects of TH deficiency on GABA show complexity in neonatal and adult life as induction of neonatal hypothyroidism by $^{131}$I injection decreases GABAergic function in neonatal developing rat brain [92], but in contrast, $^{131}$I injection to adult rats to induce adult-onset hypothyroidism impair the exchange of glutamate, glutamine and GABA between neuronal and glial compartments and increase GABA concentration [93]. Results similar to those reported in adult rats were also observed when adult-onset hypothyroidism was induced by intraperitoneal carbimazole [94]. This increase in GABA following adult-onset hypothyroidism is consistent with reports showing that GAD activity...
increased in the visual cortex following hypothyroidism[95]. Induction of hyperthyroidism by intraperitoneal T4 injection is shown to decrease GABA and increase glutamate levels in the thalamus and hypothalamus [94]. In addition, an in-vitro study on brain synaptosomes revealed that low nanomolar concentrations of T3 could increase depolarization-induced GABA release through a direct, non-genomic mechanism[96]. It is thought that this T3 induced GABA release is achieved via a direct non-genomic effect of T3 which increases Ca^{2+} uptake by the synaptosomes[97]. Based on the presented evidences, it can be summarized that THs differentially regulate the GABAergic system. THs induce or increase GABA function in developing brain, but oppose it in matured brain. This linkage presents a new field of research to elucidate if the effects of THs on GABAergic systems contributes to the pathogenesis of epilepsy.

Interestingly, researches have proved that GABA also modulates thyroid system function [91]. Generally, GABA inhibits thyroid function at all three levels of the hypothalamus, pituitary, and thyroid axes (Figure 2)[91]. Beside this bidirectional interplay between GABA and THs, GABA also plays an important role in seizure suppression as an inhibitory neurotransmitter. Thus, in contrast to adult brain, it can be presumed that THs inhibits seizures by increasing GABAergic system during brain development.

![Diagram of the hypothalamic-pituitary-thyroid axis and GABAergic system interactions](image)
6. Thyroid hormones, epilepsy and participant genes

Different studies have found a set of genes whose products might be affected by THs or influence its function. These set of genes are also found to be affected in a variety of other situations such as epileptic seizures. Here, an attempt was made to provide a brief review on latest evidences about the genes associated with THs which are also implicated in epileptic situations.

A group of factors that are influenced by THs and their dysregulation could participate in epileptic conditions is neurotrophins and nerve growth factors. It has been demonstrated that in seizures induced by amygdala-kindling, expression of neurotrophins could be changed; on the other hand, THs has also been shown to modulate the expression of these factors. Investigating the expression of neurotrophins following the depletion of THs has shown that while the expression of BDNF mRNA in the hypothalamus and pituitary gland increased, the expression of NGF and NT-3 mRNA did not change. In this study, amygdala-kindled seizures decreased the expression levels of NT-3 mRNA in granule cell layer of the dentate gyrus, which interestingly was reversed by THs replacement [98].

In addition, a number of studies have been published showing that gene expression of thyrotropin-releasing hormone (TRH) and its receptor are affected by seizures suggesting that TRH might play a role in the pathogenesis of epilepsy [99, 100]. Neuropeptide Y (NPY) is another factor that is closely associated with THs. On one hand, NPY is shown to negatively modulate TSH/T4 concentration [101] and on the other hand, it has been shown that seizure induction alters the expression of NPY and different NPY receptor subtypes [102, 103].

Proteomic studies on cerebrospinal fluid (CSF) obtained from TLE patients have shown an increase in vitamin D-binding protein (DBP), indicating that this protein might be involved in the pathology of epilepsy [104]. This binding protein and its partner vitamin-D are also shown to contribute to thyroid pathologies like thyroid autoimmune diseases and thyroid tumorigenesis [105, 106]. Another set of genes that participate in the process of epileptogenesis and are also affected by THs are some of the immediate early genes (IEGs) like Homer1, early growth response 1 (egr1) and activity-regulated cytoskeleton-associated protein (Arc). Prenatal propylthiouracil (PTU)-induced hypothyroidism
decreases the hippocampal and cortical expression of immediate early genes and indicates their involvement in brain defects caused by developmental hypothyroidism [107]. The immediate early genes on the other hand are shown to be over-expressed in different regions of the hippocampus and cortex of epileptic animals and therefore may play a significant role in seizure-induced synaptic reorganization[108, 109].

7. Thyroid hormones, gender differences, sex steroids, and epilepsy

The role of sex hormones in the development of animals cannot be overlooked, especially when it comes to development of the brain and the central nervous system. It is well evident that sexual differentiation of the brain leads to lasting changes in its structure and function. This process to a great extent is under the influence of sex and other circulating hormones, as well as the interaction of the environment and the developing neurons; nutrients, medication and other chemical substances are also able to influence the process [110].

Epidemiological studies have suggested that males have a slightly higher incidence of epilepsy and unprovoked seizures compared to females. Though it seems that males are at greater risk than females for seizures and epilepsy, this is not applicable for all types of epilepsies. For instance, idiopathic generalized epilepsies (IGEs) have a higher prevalence in females [111]. Several lines of evidence show that sex hormones, beside their roles in brain development are also involved in the regulation of neuronal excitability and survival. Fluctuations in sex hormones could affect the pathogenesis of epilepsy and furthermore, seizures affect the function of the sexual endocrine system (reviewed in [10]). As mentioned earlier, THs are of special importance in the process of brain development and therefore, it is conceivable to assume that sex hormones and THs interact with each other during brain development. Accordingly, it is reported that hypothyroidism prolongs the critical period for the defeminization process induced by testosterone; on the other hand, hyperthyroidism leads to premature termination of testosterone sensitivity [112].

Like steroid hormones, THs, steroids interact with their receptors to alter genomic activity and affect protein synthesis during development and other stages of life. As is the case with T4, the metabolic transformation of testosterone and progesterone is critical for their actions. In addition, THs and sex steroid hormones differentially alter brain functions in adults when compared to the developmental stages [113-115]. Another important factor that demonstrates the relation and interaction between steroids and THs is the thyroid hormone receptor-associated protein (TRAP220). TRAP220 is a coactivator for nuclear receptors, recruits TRAP mediator complex to the hormone responsive
promoter regions and stimulates gene transcription. In other words, TRAP220 enhances the function of TRs, steroid hormone receptors, retinoic acid receptor α and vitamin D receptor [116, 117]. Decreased TRAP220 mRNA levels in epileptic tissue can be an indicator of the role that TRAP220 plays in the neuropathology of epileptic seizures [118]. In other studies, both the gene and protein expression level of TRAP220 in brains of epileptic patients were measured. The focus was on the temporal lobes of patients with chronic pharmaco-resistant epilepsy who underwent surgery. The results showed that expression of TRAP220 mRNA in the temporal cortex was significantly reduced in epileptic patients both in mRNA and protein levels. This decrease might affect the pathophysiology of epilepsy and may be related to subsequent brain damage after frequent seizures [119, 120].

Another important factor involved in the interaction between THs and steroids is the type 3 deiodinase or D3, which is necessary for the maturation and function of the brain. D3 has distinctively high expression in the brain of newborn rats and usually occurs in those areas of the rat brain which are involved in sexual differentiation [113, 121]. D3 deficiency profoundly alters THs availability before and after birth and increases its availability during the perinatal period [122-124]. D3 protects the brain from high doses of T3 by reducing its effects. D3 itself is also regulated by the effect of thyroid hormones on the TRα1 receptor subtype [125, 126].

It has also been indicated that development of CNS and sex hormones are important factors in the susceptibility of the brain to seizures. Seizures in general and epileptic seizures in particular are more likely to develop in the immature brain. Male infants and newborns are more likely to experience epileptic seizures or develop an unprovoked seizure than females. Sexual differences which are expressed in the development of seizure-suppressing neuronal networks can be considered as one of the reasons behind this susceptibility [127]. These observed differences are mostly linked to the type of epileptic disorder. For instance, gender difference was identified in idiopathic generalized seizure in two population-based studies; in an outpatient study, the differences were attributed to gender differences in juvenile absence epilepsy and juvenile myoclonic epilepsy [128, 129]. As previously mentioned, females in general are at a greater risk of IGEs, which is probably because of the effects of sex hormones. This assumption is supported by the observation that IGE is more likely to occur in females between the ages of 15-50 and before menopause [111, 130, 131]. Among patients with cryptogenic localization-related epilepsy, women were more frequent. Therefore, it seems that non-symptomatic epilepsy more often occurs in women in contrast to symptomatic localization-related epilepsy, which has preponderance in men.
On the other hand, males may be more vulnerable to brain damage induced seizure[132], and development of generalized tonic–clonic seizures [133]. They are also more susceptible to develop symptomatic localization-related epilepsy which can be attributed to higher risk of physical damage to the brain and the consequent seizures [128, 134]. The differences between genders are mostly expressed in ages30-59; which is the age range for higher TBI risks. Males are also more probable to experience brain damages accompanied with seizures [135, 136]. A gender dependent difference has also been reported in childhood absence epilepsy [137, 138]. A quantitative analysis showed that there is a sex difference in the number of spines and primary dendrites on the apical CA3 pyramidal cells of the hippocampus. In this study, females possessed more primary dendrites while males showed more apical excrescences and interestingly, neonatal treatment with thyroid hormone resulted in long-lasting and dramatic changes in the entire CA3 pyramidal cells [139].

8. Antiepileptic drugs and thyroid hormones

Several lines of evidence show that antiepileptic drugs (AEDs) affect different aspects of THs hemostasis such as biosynthesis, release and transport as well as metabolism in both children and adults [reviewed in [140]]. In this regard, in 1981 Strandjord et al. reported for the first time that treatment with some AEDs could affect thyroid function [141]. In accordance, Yilmaz et al. have evaluated the effects of widely used AEDs on thyroid function in children with new onset and controlled epilepsy. They reported that during a 12-months period of therapy, all AEDs except levetiracetam increased TSH level and decreased fT4 concentration [142]. In another study, it was reported that carbamazepine monotherapy in epileptic children and adult patients impaired thyroid function [143].

Evidence is also available showing that AEDs affect the cellular mechanism of TH functions. For instance, a single injection of diazepam (a benzodiazepine) after 24h affects nuclear T3 binding and relative expression of TH receptor TRα2 but not TRα1 and TRβ1 and synaptosomal TH availability [144]. Alternatively, THs also modulate in-vivo and in-vitro binding of benzodiazepines on their specific membrane receptors [145, 146]. These results raise the risk of using AEDs in patients with TH deregulation [147]. It must be emphasized that AEDs-induced alteration in thyroid function is not permanent and could be reversed by termination of their intake. For instance, it was reported that the serum level of fT4 increased 4 months after withdrawal of carbamazepine in epileptic men and women [148].
Interestingly, thyroid function is also sensitive to drugs used to induce seizure in experimental models. In this regard, Bolaris et al. investigated if central responses to THs are affected by a single convulsion dose of pentylenetetrazole (PTZ). Their results showed that 4h after PTZ-induced seizures, the density of specific T3 nuclear receptors increased in the cerebral hemispheres while the non T3 binding receptor (TRα2) decreased. These effects were associated with an increased synaptosomal T3 level during epileptic seizures[149].

9. Conclusion

Although the complete pathogenesis of epilepsy still remains to be elucidated, it is well demonstrated that mitochondrial dysfunction, oxidative stress and deregulation of GABAergic system play pivotal roles in this process. In spite of the fact that BBB impedes the access of THs to the CNS and limits the concentration of these hormones compared to that of serum, researches have now shown that THs play essential roles in different physiological aspects of the CNS such as development, normal brain function and repairing machinery. Molecular evidences have shown that THs participate in normal mitochondrial biogenesis and lack of their function causes mitochondrial dysfunction and oxidative stress. In addition, it is well evidenced that the development and function of GABAergic neurons depends on normal THs function. A massive body of knowledge has been gathered over the past decades to support the positive effects of THs on neural cells regeneration. However, BDNF, one of the most important neurotrophic factors influenced by THs, seems to cause detrimental effects on the development and aftermaths of epilepsy. Nevertheless, most collected evidence and knowledge are in favor of the positive effect of THs and there is no doubt that THs play a significantly influential role in various aspects of epilepsy, from development to healing and recreation. However, different theoretical ways by which THs are believed to contribute to the pathologies of epilepsy should be further clarified.

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