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Possible Role Of Thyroid In Epilepsy

Ghisulal Dewasi

Pharm.D, Bhupal Noble's University, Udaipur, India grraika06@gmail.com

ABSTRACT

Thyroid hormone is produced by the thyroid gland. There are two types of thyroid hormone T3(triiodothyronine) & and T4 (thyroxin). They are tyrosine derivatives. They play an important role in the development of CNS and regulate metabolism in our body. Any thyroid hormone deficiency at an early age can lead to neurological dysfunction in adults. These neurological dysfunctions are irreversible. Thyroid hormones also control the development of GAB Anergic neurons. Thyroid hormone inhibitory or excitatory action can cause seizure generation in humans, but there are no significant shreds of evidence about it many hypotheses and studies are available about this. Epilepsy is characterized by seizure episodes, the pathophysiology is associated with mitochondrial dysfunction, oxidative stress, and impairment of GABA neurons. On recent evidence, we can hypothesize that thyroid hormone abnormality can cause epilepsy.

Keywords: Thyroid hormone, Epilepsy, Seizures, GABA Neurons, Brain development, Hypothyroidism

I. INTRODUCTION

Thyroid hormone is a hormone that is secreted by the thyroid gland which is located in the neck region.

Thyroid hormone plays a vital role in metabolism. Thyroid hormone is composed of two hormones T3 triiodothyronine and T4 thyroxin(1). These hormones are responsible for gene expression. T3 and T4 hormones regulate cell development, homeostasis, and metabolism. The thyroid hormone plays a vital role in brain development In fetal and maintenance of the adult brain as well (2). Thyroid hormone regulates CNS functions in adults as well as in neonates. Failure in the regulation of glutamate and GABA amino acids leads to seizure generation (3).

Mitochondrial dysfunction, oxidative stress GABAnergic deregulation are the main characteristics of epilepsy which are also associated with hypothyroidism. (4) The review provides information about the possible role of the thyroid in epilepsy.

II. THYROID HORMONE:

Thyroid hormone is secreted by the gland thyroid. The thyroid hormone consists of two hormones T3 & and T4. Thyroid hormone release is controlled by the hypothalamic-pituitary-thyroid axis (HPTA). The secretion of the thyroid is stimulated by thyroid stimulating hormone which is secreted by the pituitary gland and is regulated by thyrotropin-releasing hormone which is released by the hypothalamus gland. T3 hormone is a deionated form of T4 which is more potent. (5)

III. THYROID HORMONE IN CNS:

Thyroid hormone targets the central nervous system. The thyroid plays a vital role in brain development in neonates and adults and maintains many physiological functions. Thyroid hormones have poor penetration across the blood-brain barrier so the concentration in serum is more than CNS tissue. Two main pathways explain how thyroid hormone crosses the BBB. In 1st pathway, thyroid hormone crosses BBB by OATP1C transporters and enters into astrocytes' end feet. Now the T4 converts into the T3 hormone. In 2nd pathway, MCT8 transporters help the thyroid hormone to cross the BBB. There are gaps between the BBB where astrocyte ends feet are not covered by capillaries, through these gaps thyroid hormone also enters(6). The activity is triggered by binding to the TRs.

Functions of thyroid hormone in CNS:

Several forms of thyroid receptors are found in mammals like TRα1, TRα2, TRβ1, TRβ2a, and TRβ3, but TRα1, TRβ1, TRβ2a, and TRβ3 are the main functional receptors. TRα1 is the main receptor that helps in brain development. (7). There are some important functions of the thyroid gland in CNS:

Thyroid hormone contributes to the formation of neural connections, differentiation of neurons, and the growth of dendritic processes.

Thyroid hormone is responsible for promoting proper brain growth, including the proliferation and migration of nerve cells, hypothyroidism can cause severe brain issues.

Myelin, the fatty substance which is the outermost cover of nerve cells that transmit the signals is not formed properly in hypothyroidism.

Serotonin, dopamine, and norepinephrine are the neurotransmitters in the brain. Thyroid hormone promotes the formation & and metabolism of these neurotransmitters. These neurotransmitters regulate mood, cognitive functions, and overall CNS activities.

Thyroid hormones play a vital role in CNS regulation and the overall health of the CNS system. Hypothyroidism leads to brain dysfunction in severe cases (8).

IV. Epilepsy

Epilepsy is a disorder characterized by repeated seizures this is due to the continuous excitation of neurons. In the majority, the cause of epilepsy is unknown, and the remaining have multiple causes like mitochondrial dysfunction, oxidative stress, tumors, metabolic imbalance, and many more. Cerebral cortex development is also the cause of epilepsy (9). Thyroid hormone dysregulation is the main cause of epilepsy.

V. Thyroid Hormone, Adult CNS and Epilepsy

In adults, brain injury is the main cause of epilepsy, and patients with brain injury have lower thyroid levels. Trauma causes brain injury, and patients with traumatic brain injury have defective thyroid hormone metabolism which means T4 to T3 hormone conversion is impaired. (10). Myeline, the fatty layer that regulates sensory information also affected by low thyroid hormone levels. During pregnancy and lactation reduced levels of thyroid hormone can cause audiogenic convulsions. (11) Thyroid hormones affect the genes, in which neurotrophic factors significantly play a role in pathophysiological conditions such as seizures (12). Neural excitability, synaptic plasticity, neurotransmitter synthesis, neural differentiation, survival, and growth all are exerted by neurotrophic factors(13). Neurotrophic factors that influence the seizures:

1)fibroblast growth factor -2 (FGF-2)

2) Brain-derived neurotrophic factor (BDNF)

3) neurotrophin-3 (NT-3)

4) nerve growth factor (NGF)

5) glial cell line-derived neurotrophic factor(GDNF)

6) Vascular endothelial growth factor (VEGF) (14)

Some studies show that increased expression of neurotrophic factors or acute seizures contributes to immunomodulation of the injured brain (15).

VI. Thyroid hormone and epileptogenesis

Thyroid hormone and mitochondria:

We already know that oxidative stress, mitochondrial dysfunction, trauma, and free radicals are responsible for seizure generation (16–18). Thyroid hormones affect mitochondrial function and can be genomic or nongenomic (18). There are three different pathways through thyroid hormone regulates the targeted genes and biogenesis of mitochondria. In the first pathway T3 hormone directly affects the mitochondria

by attaching to mitochondria-localized receptors (19). A gene named P43 is present in the mitochondria inner membrane which gives a binding site to the T3 hormone. Overexpression of the P43 genome leads to high protein synthesis and mitochondrial transcription (19). In the second pathway, T3 binds to nuclear-localized thyroid receptors and TREs and controls the gene expression of nuclear-encoded protein synthesis that eventually affects mitochondrial biogenesis. (19). peroxisome proliferator-activated receptor gamma coactivator 1-alpha, peroxisome proliferator-activated receptor gamma coactivator 1-beta. Now these co-activators enter into mitochondria and interfere with mitochondrial biogenesis (20). T3 increases the oxygen supply and ATP hydrolysis. Hypothyroidism is associated with high oxygen consumption in most of the tissues except the brain and testicles(21,22). The high oxygen consumption is associated with proton leak. Firstly T3 hormones interfere with mitochondrial phospholipid layer composition and its permeability(23). Due to this mitochondrial coupling proteins are formed while ATP synthesis is leaked from the membrane which increases the oxygen permeability. On the other hand, when thyroid hormone levels decrease the function and biogenesis of mitochondria are affected largely (19). Degranulation of glutamate-glutamine-GABA cycling was also observed in neurons due to impairment of mitochondrial metabolism which is epileptogenic (24,25). Concluded that the dysfunction of mitochondria can cause epilepsy but there are need for more studies that can prove this hypothesis.

Thyroid Hormone and Oxidative Stress:

The imbalance between oxidant agents and antioxidant activities of the defense system in the body is known as oxidative stress(26). An adult brain uses 20 to 35 % oxygen of the body and 25% glucose of the body (27). Mitochondria uses oxygen to produce ATP, however, 1 to 2 % of oxygen is incomplete and produces superoxide. In the presence of free iron radicals, these superoxides have a high chance of reacting with hydrogen peroxide and forming hydroxyl superoxide if these superoxides are not destroyed immediately. This hydroxyl superoxide is commonly known as reactive oxygen species(ROS). These ROS can attack biomolecules such as DNA, Protein, and Lipids, this process is known as oxidative stress(28).

Some studies show that ROS can play a role in epileptic seizures(29). Hypothyroidism or hyperthyroidism can help in the formation of ROS. The dysregulation of thyroid hormone leads to an imbalance of oxidative and antioxidative agents. (30)

Mitochondrial DNA is mainly affected by oxidative stress because this has direct contact with superoxides, however, the nuclear DNA has protection of histone complexes but mtDNA has no such protection. Brian has a poor antioxidant defense system which makes it more susceptible to ROS. Which can easily lead to epileptic seizures. (30)

Thyroid hormone and GABAnergic Neurons

Thyroid hormone modulates the regulation of GABAnergic neurons (5). Study shows that when the T3 hormone is injected into a fatal rat brain, the activity of the glutamic acid decarboxylase enzyme significantly increases, and that enzyme converts glutamic acid into GABA(31). Thyroid hormone also affects the enzymes that participate in GABA metabolism like GABA transaminase and succinate semialdehyde dehydrogenase which affects the GABA life cycle.

In hypothyroidism, GABA-generating and destroying enzymes are mainly affected. Due to thyroid hormone deficiency GABAnergic interneurons get impaired which leads to locomotor dysfunction and anxiety disorders (8,32). Thyroid hormone deficiency leads to GABA impairment which ultimately contributes to epileptogenesis.

VII. Participant genes:

Multiple genes are affected due to thyroid hormone deficiency. Those genes that are affected in epilepsy also can affected by thyroid hormone deficiency. Neurotrophins and nerve growth factors are the genes that are affected due to deficiency of thyroid hormone and contribute to epileptic seizures. In amygdala kindling seizures, the expression of neurotrophins could be changed, and studies show that thyroid hormone also can affect these genes. Amygdala seizures decrease the expression of NT-3 and mRNA in granule cells of dentate gyrus, interestingly this can be reversed by thyroid hormone replacement (33). Seizures also affect the thyrotropin-releasing hormone genes and receptors which ultimately reduce the secretion of thyroid hormones (34). Neuropeptide Y is also a gene that is associated with this, NPY negatively modulates the thyroid hormone, and seizure production alters the expression of the NPY gene (35–37). Some studies have shown that patients with temporal lobe epilepsy (TLE) have increased vitamin D binding protein which means this protein might be involved in epileptogenesis (38). Immediate early genes (IEG) are the group of genes that are involved in epileptogenesis and are also affected by the thyroid hormone. Prenatal propylthiouracil-induced hypothyroidism decreases the hippocampal and cortex expression of immediate early genes (39).

VIII. Thyroid hormone and antiepileptic drugs

Antiepileptic drugs affect biosynthesis, homeostasis, release, transport, and metabolism in adults as well as in children (40). Treatment with carbamazepine in children and adults causes thyroid dysfunction (41). Several studies have shown that antiepileptic drugs affect the thyroid hormone. AEDs affect the cellular mechanism of the thyroid hormone. Levitiracetam increases the level of TSH level and decreases the level of T4 concentration (42). These effects on the thyroid hormone are dose-dependent, these are not permanent.

IX. Conclusion

Pathogenesis of epilepsy remains unclear but it is demonstrated that oxidative stress, mitochondrial dysfunction GABAnergic system play a vital role in epileptogenesis. Nowadays many research have shown that thyroid hormone is essential for brain development in adults and neonates. The thyroid hormone regulates the biogenesis of mitochondria, low thyroid hormone level causes dysfunction of mitochondria and oxidative stress. Thyroid hormone significantly influences epilepsy development.

REFERENCES

1. Cleveland Clinic [Internet]. [cited 2023 Aug 26]. Thyroid Hormone: What It Is & Function. Available from: https://my.clevelandclinic.org/health/articles/22391-thyroid-hormone

2. Escobar GM de, Obregón MJ, Rey FE del. Maternal thyroid hormones early in pregnancy and fetal brain development. Best Pract Res Clin Endocrinol Metab. 2004 Jun 1;18(2):225–48.

3. Tsai HL, Chang CN, Chang SJ. The effects of pilocarpine-induced status epilepticus on oxidative stress/damage in developing animals. Brain Dev. 2010 Jan 1;32(1):25–31.

4. Tamijani SMS, Karimi B, Amini E, Golpich M, Dargahi L, Ali RA, et al. Thyroid hormones: Possible roles in epilepsy pathology. Seizure. 2015 Sep 1;31:155–64.

5. Gilbert ME, Lasley SM. Developmental thyroid hormone insufficiency and brain development: A role for brain-derived neurotrophic factor (BDNF)? Neuroscience. 2013 Jun 3;239:253–70.

6. Schroeder R. Transitioning Students Transforming Higher Education. OLA Q. 2014 Apr 30;20(1):40–3.

7. Bernal J. Thyroid Hormones in Brain Development and Function. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2023 Aug 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK285549/

8. Borges K, Gearing M, McDermott DL, Smith AB, Almonte AG, Wainer BH, et al. Neuronal and glial pathological changes during epileptogenesis in the mouse pilocarpine model. Exp Neurol. 2003 Jul 1;182(1):21–34.

9. Bondanelli M, Ambrosio MR, Zatelli MC, De Marinis L, Uberti EC degli. Hypopituitarism after traumatic brain injury. Eur J Endocrinol. 2005 May 1;152(5):679–91.

10. AUDIOGENIC SEIZURES IN RATS AFTER SEVERE PRENATAL AND PERINATAL IODINE DEPLETION | Endocrinology | Oxford Academic [Internet]. [cited 2023 Aug 27]. Available from: https://academic.oup.com/endo/article-abstract/100/1/242/2617848?redirectedFrom=fulltext fm.2011.36