REVIEW

The hypothyroid brain

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The thyroid gland is controlled by a feedback system, the hypothalamus-pituitary-thyroid axis, and produces thyroid hormone (TH), which plays a critical role in growth, development and cellular metabolism. Diseases of the thyroid are well defined clinically and biochemically and diseases affecting thyroid function can cause both clinical hypothyroidisms, the most common cause of thyroid dysfunction, occurs when there is a decrease in the production of thyroid hormones, and hyperthyroidism, when there is an increase in hormone production. Common systemic manifestations of hypothyroidism include fatigue, dry skin, weight gain, hair loss, cold intolerance, hoarseness and constipation. Patients affected by this condition present a number of central and peripheral signs in the nervous system that may be neurological manifestations that occur along with the systemic disease. The conversion of thyroid hormone in the target tissue is done by three distinct deiodinases: type I, type II and type III. Each deiodinase has a different function in order to maintain thyroid hormone homeostasis in the tissues. Other proteins important for thyroid state are the TH transporters. MCT8, OATP1C1 and LAT1 and 2 transporters regulate T4 and T3 flow in the cells. The action of THs depends on the interaction of several proteins that are specialized in the control of thyroid hormone homeostasis not only in the brain but also in various tissues. THs are important for the maturation of the brain from the intrauterine period and remain important to adulthood. When there is some disturbance in the control mechanisms for the state of thyroid hormone, the consequences to the tissues, especially the CNS, can range from mild damage to severe impairment in neuronal development.

Keywords: Hypothyroidism; brain; receptor; transporter; deiodinase

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Introduction

The thyroid, like other endocrine glands, is controlled by a classic feedback system, the hypothalamus-pituitary-thyroid axis [1, 2]. And the hormone it produces, thyroid hormone (TH), plays a critical role in growth, development and cellular metabolism. Diseases of the thyroid are well defined clinically and biochemically and diseases affecting thyroid function can cause both clinical hypothyroidisms, when there is a decrease in the production of thyroid hormones, and hyperthyroidism, when there is an increase in hormone production. Hypothyroidism, the most common cause of

thyroid dysfunction, is caused by iodine deficiency and more frequently by Hashimoto's thyroiditis. Conversely, the most frequent cause of hyperthyroidism is toxic diffuse goiter or Graves' disease, followed by autonomous nodes (Plummer's disease). Hypothyroidism affects the general population and is a common medical condition. Common systemic manifestations of hypothyroidism include fatigue, dry skin, weight gain, hair loss, cold intolerance, hoarseness and constipation. Patients affected by this condition present a number of central and peripheral signs in the nervous system that may be neurological manifestations that occur along with the systemic disease. Such manifestations may be partially or fully corrected using thyroxin. In this review, we focus on hypothyroidism and brain development.

Hypothyroidism

Iodine deficiency and thyroiditis, such as Hashimoto's thyroiditis, are the main causes of hypothyroidism [3].

Hashimoto disease is an autoimmune disease of the thyroid gland caused by auto antigens developed against the gland and triggered by environmental exposure to certain factors, such as smoking, alcohol, selenium [4], and iodine intake [4, 5] in genetically predisposed individuals. In Hashimoto's disease the gland gradually atrophies, then the immune system cells (lymphocytic cells) attack the tissue, resulting in follicular atrophy, which triggers hypothyroidism [6].

Iodine deficiency used to be a serious public health problem and significant cause of intellectual disability. During the 20th century a battle was waged to eradicate these disorders; however, in certain parts of the globe, the problem still exists [7]. Iodine, a trace element, is indispensable for thyroid hormone synthesis, and must be acquired via food intake. A deficiency in this element results in the malfunction of the thyroid gland, hypothyroidism and neurodevelopmental disorders [8].

Congenital hypothyroidism (CH) is the most common pediatric endocrine disorder and its clinical diagnosis and treatment is very important right from birth, since severe cases can lead to irreversible mental impairment [9]. CH prevalence ranges from 1:2000 to 1:4000 cases in newborns [3, 10]. CH is caused by thyroid gland development disorders, which may be associated with TSHR, PAX8, NKX2.1 and FOXE1 gene mutations (representing 80-85% of cases) and, thyroid gland hormonal synthesis problems (representing 15-20% of cases), and may also be associated with mutations in the following genes: DUOX2, TG, TPO, SLC5A5, SLC26A4 and IYD [10, 11].

Hypothyroidism can be caused by a disruption on any level of the hypothalamic-pituitary-thyroid axis. These new forms of hypothyroidism, which are rare, have been diagnosed using molecular biology techniques. Changes related to hypothalamic TRH and pituitary changes in factors, such as Pit-1, are thought to cause central hypothyroidism. Nevertheless, central hypothyroidism may also be due to thyrotoxicosis caused by adenomas and this may decrease tissue sensitivity to thyroid stimulating hormone (TSH). Hypothyroidism may also be related to mutations in the hormone receptors in the target tissue. The mutated receptor has an impaired ability to bind to the active thyroid hormone [12, 13].

Subclinical hypothyroidism

Subclinical hypothyroidism (SCH) can lead to hypothyroidism, and be a risk factor in losing thyroid gland function completely, which can be addressed by increasing TSH levels [14]. SCH is characterized by an increase in TSH levels that can range from 4.0 to 10.0 mIU/l in milder SCH and TSH >10.0 mIU/l in severe SCH [15, 16]. Notwithstanding, SCH patients may present positive anti-thyroid peroxidase (TPO) antibodies, as well as a TSH level of between >2.0 mIU/l and <10.0 mIU/l [17]. Although mild SCH patients do not present symptoms of hypothyroidism, Canaris and coworkers [18] found a small difference in hypothyroidism symptoms between euthyroid and SCH patients, such as muscle cramps and weakness and dry skin [18, 19].

Hashimoto's thyroiditis is considered to be the most common cause of endogenous SCH [20]. Other endogenous and exogenous causes may include: loss of TSH receptor function due to mutation; recent adjustment of levothyroxine dose; high transient level of TSH during recovery from a serious illness and sub-acute or postpartum thyroiditis; untreated primary adrenal insufficiency; during treatment with various drugs (lithium, amiodarone, recombinant human TSH injections); and the presence of heterophile antibodies [15].

Treatment of hypothyroidism and SCH

The treatment of hypothyroidism depends on its causes. Iodine deficiency in the diet can cause the thyroid gland to malfunction, and is a major cause of brain damage in the world [21]. Supplementation of iodine should be done through food. In many countries there is mandatory supplementation of this element in salt [22].

When hypothyroidism is caused by a deficiency of the hormone due to thyroiditis, congenital hypothyroidism or thyroidectomy, the dosage of TSH is set so this hormone is

maintained at a regular concentration. Levothyroxine is used to regulate the hypothalamic-pituitary-thyroid axis and defining its dosage will depend on the results of serum concentration of TSH [23].

Treatment with levothyroxine is usually recommended when the TSH level is higher than 10.0 mIU/l. However, the available evidence on the risks and benefits of treatment for patients with TSH <10.0 mIU/l (light SCH) remains controversial and there is still no consensus on the clinical importance of adverse events and the benefits of treatment with thyroxine in patients with TSH <10.0 mIU/l. One reason may be that all the studies that assess the adverse effects had SCH patients with different levels of TSH and thyroid dysfunction. So questions still remain about the treatment of SCH [15, 17].

Thyroid hormone and tissue metabolism

The conversion of thyroid hormone in the target tissue is done by three distinct deiodinases: type I, type II and type III [24, 25]. Each deiodinase has a different function in order to maintain thyroid hormone homeostasis in the tissues. Type 2 deiodinase (DIO2) has a high affinity for T4, the tissues in which it is most expressed are: brain, brown fat, pituitary [26, 27]. Together with DIO2, DIO1 regulates the level of T4 and T3 [28]. Other proteins important for thyroid state are the TH transporters. MCT8, OATP1C1 and LAT1 and 2 transporters regulate T4 and T3 flow in the cells [29].

The thyroid gland produces more T4 (80%) than T3, but the receptors have greater affinity to T3, which is considered the active form of the hormone. This affinity to T3 may be 10-15 times greater than to T4, so to have deiodinases working properly in the target tissues is very important [30, 31]. The level of occupation of the receptors by T3 varies from one tissue to another, e.g., in the brain receptor saturation occupation can reach 75% while in the liver this value is 50% [30, 31]. TH receptors are associated with DNA, regulating the expression of genes responsive to the hormone [30; 31; 32].

Thyroid hormone and the central nervous system

The proper functioning of an organ executed by THs is possible since the functioning of thyroid hormone homeostasis is tissue-specific. Therefore, local control is critical, and deiodinases, transporters and receptors modulate this fine control [33].

Thyroid hormones, produced by the thyroid gland, are responsible for the growth and development of several organs, and the homeostasis of the central nervous system (CNS) is one of these organs [34, 35, 36]. The actions of thyroid hormones (THs) are possible due to specialized proteins, members of a family of nuclear receptor hormones, THRα1, THRβ1 and THRβ2, that are encoded by THRa and THRb genes, respectively; these genes undergo alternative splicing to form each isoform [37]. The most expressed TH receptor in the brain is THRα1, which comprises 70% to 80% of the THR expression in the adult brain in vertebrates; this receptor is present in almost all neurons [38]. It is also important to point out the importance of two other proteins involved in TH status in the brain, the enzyme responsible for TH activation, deiodinase type 2 (DIO2), and the expression of a TH transporter, monocarboxylate transporter 8 (MCT8), both are fundamental for the interaction of neuron and glial cells [39].

THs are important to neurogenesis, especially during prenatal neurodevelopment [39]. The hippocampus is a structure in the brain that retains its plasticity throughout adult life [40]. Some clinical features have already been associated with TH deficiency, such as mood, cognition, attention and depression [19, 41, 42].

In the 1960s a link was made between depression and thyroid disorders, since many patients who were treated with antidepressants often only obtained improvements after they started supplementation with TH [43, 44]. Together, it is believed that some patients suffer from central hypothyroidism, a condition that is associated with inappropriate TH transport, inappropriate deiodination and inappropriate response of the receptors [45, 46].

A lack of TH can induce not only peripheral deficiency of the hormone, but also clear cases of hippocampal hypothyroidism, characterized by a significant decrease in the expression of important genes associated with thyroid metabolism, such as MCT8 and THR α1 [47]. As already reported, the thyroid hormone influences mood and behavior through several molecular bases whose origins are not fully understood [48].

DIO 3 deficient animals present a series of negative consequences, since the clearance of TH is affected and there is an excess of T3 [49]. A recent study conducted by Patrizia Stohn *et al.* [50] showed that knockout animals for DIO3 that were also knockout for MCT8 presented defects only when deficiency of DIO3 was attenuated. Moreover, the combined knockout MCT8 and DIO2 led to effects similar to hypothyroidism [51].

Hypothyroidism and SCH are both associated with impairments of mood, cognition and memory [15, 52]. Despite conflicting results from studies that show a relationship

between the neuropsychological development defects resulting from a pregnancy in which SCH was detected, studies have also shown that a slight increase in TSH in early pregnancy could indeed harm the intellectual development of offspring [53, 54, 55].

Secretion of THs by the fetus starts around 18 weeks of pregnancy, but T4 and T3 can be detected in the human cerebral cortex by week 12 of gestation. This is evidence that there is transport of THs from the mother through the placenta. This shows the need to maintain maternal T4 levels to ensure the development of normal fetal brain [56].

During pregnancy, an adequate supply of maternal THs should be maintained to ensure the normal neurological development of the fetus [57, 58, 59, 60]. Reduction of the maturation of key structures, such as a delay in the maturation and migration of granule cells and Purkinje cells in cerebellum, were detected in TH deficiency [56, 61, 62]. The absence of THs in early life causes damage to CNS development with severe mental retardation and neurological disorders such as ataxia, incoordination, strabismus, deafness and sensor neural hearing loss [63, 64]. TH is important in the regulation of myelination [65], mitochondrial gene expression [66] and genes responsible for intracellular signaling [67].

Lack of THs caused by problems in the development of the thyroid gland and inadequate iodine intake is the most common cause of neurological disability, making the replacement of these hormones as early as possible to decrease damage to the CNS in these children extremely important [68]. Moreover, recent evidence suggests that even moderate reduction in the levels of THs in early pregnancy (first trimester) is associated with reduced IQ in offspring. Changes in brain development in rats with hypothyroidism are mainly observed in the postpartum period [69].

Pregnancy is a very sensitive period and the thyroid gland increases by 10% of its original size in women from countries where iodine deficiency is present. Demand for the thyroid hormone increases by 50% and this situation is stressful on the gland and can result in hypothyroidism in women that normally have a borderline production of the thyroid hormone [70].

Deiodinases

Deiodinases are enzymes responsible for the activation and inactivation of THs, and are located in the endoplasmic reticulum, presenting a catalytic site in the lumen (DIO2), and anchored in the cell membrane with a catalytic site in the cellular compartment. They therefore have different distribution and function. In the brain, DIO2 and DIO3 are the most expressed form of these enzymes, while DIO1 is the predominant form in the cerebellum [33, 71, 72]. The function of DIO3 is to rapidly inactivate excess hormone to prevent major problems for the tissue [73]. Studies have shown that deiodinases are expressed in different cells in the central nervous system, where DIO2 is expressed preferentially in astrocytes and DIO3 in neurons, thus astrocytes generate T3 from T4, while the neuron inactivates excess hormone, generating rT3 and T2 [74, 75].

Studies in rodents have shown that 80% of the T3 present in the brain is locally produced from T4 [76], and this production is dependent on DIO2. In a hypothyroid state, DIO2 activity is increased to keep the supply of T3 at normal levels [77]. On the other hand, excess T4 inhibits the activity of DIO2 to posttranscriptional levels [78] and also acts on the mRNA [79]; in this case the excess hormone also activates DIO3.

Tanocytes are an important type of cell in the brain that helps this organ to maintain TH levels, since it expresses a high concentration of DIO2 [80]. This cell type also express MCT8 and OATP1C1, which are important TH transporters. The T3 produced in tanocytes is able to reach different regions in the brain; therefore, they are critical for brain cell homeostasis of thyroid hormones [80].

DIO2 is well expressed in astrocytes [80, 79], and in humans it is also produced in tanocytes [81] and present in oligodendrocyte progenitor cells. The T3 provided to neurons is, therefore, derived from glial cells, since neurons do not express DIO2 [75]. The deficiency in the expression of DIO2 causes a reduction in the supply of T3 in the brain, leaving the organ in a state of hypothyroidism [82]. Despite the low concentration of T3 in the brain of DIO2, the neurodevelopment, mobility, memory and anxiety of young KO mice remained very similar to the neurodevelopment and tests for control animals. Nonetheless, during adult stage, these DIO2 KO animals presented severe motor problems [71]. Some studies showed that there are proteins that balance the lack of DIO2, keeping the TH state in the brain at normal levels, by capturing T3 from circulation, when its level is normal [51, 83].

Type 3 deiodinase is responsible for the inactivation of T4 and T3, thereby controlling the concentration of T3 [84]. In the brain, DIO3 is mainly expressed in neurons. An in vitro study using astrocytes showed that this enzyme normally is not expressed in that cell type, unless there is stimulation with growth factors [85, 86]. The action of DIO3 is controlled by the concentration of T3, which acts at the transcriptional level, and the action of this T3 in the regulation of DIO3 is mediated by TH receptor TRα1 [83, 87, 88].

When production of DIO3 is deficient there is a high concentration of T3 in the perinatal period that progresses to central hypothyroidism during adulthood. In the central nervous system, the expression of genes responsive to T3 increase in the postnatal period, then throughout development follow gland parameters [49].

Thyroid hormone transporters

The brain is a sensitive organ and a major target of THs. To better protect the brain there are two barriers that restrict the passage of substances: the blood-brain barrier (BBB) and the cerebrospinal fluid (CSF) barrier. These barriers are formed by endothelial cells that only permit the passage of substances from circulation into the brain parenchyma if there are transporters for these substances [89]. Studies have shown that astrocyte cells cover capillaries and assist in the passage of substances. THs are some of the substances whose flow is controlled by transporters [90].

There are several families of proteins to which different TH transporters belong; one of them is the family of monocarboxylate transporters (MCT), in which MCT8 and MCT10 (SLX16A2 and SLC16A10 are the genes responsible for expression of these transporters, respectively) are members. These two transporters are specific to thyroid hormones; however, they have more affinity for T3 [91]. MCT8 is one of the main TH transporters, and its relevance in transporting theses hormones was highlighted by the discovery that its mutation causes a serious syndrome, which has several anomalies with serious neurological problems [92].

There are other families of TH transporters, such as the organic anion-transporting polypeptide (OATP) family, of which OATP1C1 is an important representative, encoded by the gene SLCO1C1, and L-type amino acid transporter (LAT), which is represented by LAT1 and LAT2 and transcribed by SLC7A5 and SLC7A8 genes, respectively [93].

Tissue distribution of these transporters varies. MCT8 is highly expressed in brain endothelial cells, astrocytes, tanocytes, neuronal and oligodendrocyte progenitor cells [94]. OATP1C1, which has higher affinity to transport T4 is preferentially expressed in the endothelial cells of the BBB and is also expressed in the choroid plexus [94].

Along with deiodinases, TH transporters are important to brain TH homeostasis. As previously mentioned, DIO2 is expressed by astrocytes, where T4 is converted to T3, so this active hormone is delivered to the neurons according to the needs of the tissue [75]. DIO3, preferably present in neurons, can precisely control the concentration of THs, thus maintaining the expected levels of thyroid hormones.

The mutation in MCT8, until now, was the only mutation found in human transporters that has a medical significance, since the result is devastating. Allan-Herndon-Dudley Syndrome (OMIM300523) results from an MCT8 mutation [95]. This transporter is a membrane protein decoded by the SLC16A2 gene, and this gene is located on the X chromosome [92]. The phenotype of patients with a mutation in this gene is mental retardation, delayed neurological development, delayed language development, hearing impairment, and altered levels of T4, presenting low concentrations of detected total free T4 and rT3, while total free T3 concentration is increased, although TSH is normal or moderately increased [96].

Notwithstanding, mice that were KO for MCT8, despite having high T3 and T4, and reduced rT3 concentration, presented no significant brain impairment when compared to control animals, so different mechanisms are triggered to compensate for the absence of these transporters in mice, unlike humans, who present considerable developmental consequences [97, 98].

The mechanisms that are triggered by the lack of MCT8 are: reduced supply of T4 to astrocytes, with a corresponding increase in the activity of DIO2 so the concentration of T3 may increase. Interestingly, even with an increase in type 1 (liver) and type 2 (brain) deiodinases there is a paradox in thyroid status, with a state of hyperthyroidism in peripheral tissues and a state of hypothyroidism in brain tissue [98].

TH receptors

T3 DNA binding domains are formed by two zinc fingers that are separated by an amino acid sequence which maintain their bond. The TH receptor forms a dimer with RXR, an orphan receptor [99, 100].

As previously indicated, TH receptors are encoded by two genes, THRA and THRB, and undergo alternative splicing, resulting in four different isoforms: THR α1, THR α2, THR β1 and THR β2 [31]. TR α1 is expressed primarily in skeletal and heart muscle while THR β1 is predominant in the liver, kidney and brain. THR β2 expression is restricted to nervous tissue and is present in the anterior pituitary, for example [34].

Experimental studies using knockout (KO) mice showed that when one of the specific isoforms is not expressed, the animal exhibits a different phenotype, thus showing that each receptor has its role well defined [101, 102].

Animals KO for both receptors, THR α1 and α2, had a severe hypothyroidism phenotype, presenting intestinal malformation, growth retardation and early death after

weaning [103]. When the animal was only KO for THR α1, a lighter phenotype was found, such as, low heart rate, which persisted even after hormonal supplementation (19%) [103]. These animals, KO for both α receptor isoforms, presented a high concentration of TSH and T4, increased size of thyroid gland and hearing problems [104, 105]. In patients it has been shown that resistance to TH may be due to lack of the THRα gene [106]. KO Mice to THR β2 have high concentrations of TSH and TH and vision problems, revealing the role of this isoform in the formation of retinal cone [107]. Despite the great importance of TH in the development of the organism, when a mouse strain KO for all receptor isoforms was developed, these animals were shown to be viable, even presenting striking features, such as high serum concentrations of TSH, T3 and T4, enlarged thyroid gland, and a general aspect in the development deficiency [108].

Animals that had a mutation in THR βeta showed a high concentration of T4 and TSH, light goiter, weight gain and abnormal bone development. The severity increased when the animal was homozygous, compared to the heterozygous animal. Cognitive deficiency is also a characteristic present in these animals [109, 110].

In experimental models, the presence of TH receptors is detected in embryonic period 14 (E14), even before the embryo presents a thyroid gland; in the first 6 days of the postpartum period there is an increase in these receptors [111]. The predominant isoform in the brain is THR α1, which is distributed throughout the CNS from the embryonic stage (E14) to adulthood [112].

THR α1 corresponds to 70-80% of thyroid receptors in the brain, but there is still THR β1 and THR β2 expression [113]. THR β2 is responsible for 10% of receptors in various tissues including the brain [114].

In humans, TH receptors emerged around week 10 of embryonic development and gradually increase until week 18 [115]. It is during this period that the brain increases considerably in size [116]. The main source of T3 in the fetal brain is T4, which undergoes deiodination by DIO2 [117].

The receptors are present in all cell types in the brain tissue (neurons and glial cells) [118]. They are also expressed in dorsal ganglion root, sensory neurons and transiently in Schwann cells [119].

Thyroid hormones control the expression of several genes through their nuclear receptors, but there is also the action of THs known as non-genomics, in which T4 interacts with integrin αvβ3, activating PI3K and MAPK [32]. T4, for example, participates in the expansion of progenitor cells in the neocortex acting through integrin αvβ3 act [120]. Furthermore, T3 interacts with receptors present in the neuronal cell cytoplasm and triggers maturation and plasticity of hippocampal pyramidal neurons regulating PI3K, for example [121].

In the adult brain, THs act on mood and behavior, affecting neurotransmitters [122]. Hormonal deregulation can oftentimes lead to psychiatric disorders, which can be controlled as soon as hormone levels are established [123]. Studies have shown that the use of levothyroxine as a complement in the treatment of mood disorders helps to improve the results [122]. Interestingly, a study conducted by our group, showed that animals that have undergone thyroidectomy presented antidepressant behavior due to hippocampal hypothyroidism, since genetic expression of MCT8 and DIO2 was significantly decreased, while animal behavior assessments showed no depressant behavior, corroborated by swimming test results [47].

Patients who have mutations in THR α1 suffer of deficiency in growth, bone development, severe constipation, and mild cognitive deficits, with minimal changes in thyroid hormones, normal TSH dosage, low T4/T3 ratio, low concentration of rT3, and reduced expression and activity of DIO3 [87].

The lack of THR α1 in mice has a different result when compared to animals that have a mutation in this gene. The absence of THR α1 in the brain does not resemble a hypothyroidism state. On the contrary, in a hypothyroidism state the receptor that is not bonded to a hormone, the unliganded receptor, presents activity, since the gene expression of some proteins that are negatively responsive to TH is induced [124]. On the other hand, in the absence of the receptor, this activity is suppressed and hypothyroidism is not as harmful as in its presence [125].

Conclusions

Thyroid hormone is important for the development, maintenance, and performance of the central nervous system. Both excess and lack of this hormone are harmful to this tissue. In this review, we present some of the consequences of hypothyroidism in the maintenance of CNS. We point out that the action of THs depends on the interaction of several proteins that are specialized in the control of thyroid hormone homeostasis not only in the brain but also in various tissues. THs are important for the maturation of the brain from the intrauterine period and remain important to adulthood. When there is some disturbance in the control mechanisms for the state of thyroid hormone, the consequences to the tissues, especially the CNS, can range

from mild damage to severe impairment in neuronal development.

Conflicting interests

The authors have declared that no conflict of interests exist.

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Author contributions

J.S.S. designed, wrote and revised the review; R.R.C. and K.C.O. revised and contributed with the design; R.M.B.M. and G.G. revised and corrected the manuscript. All authors approved the final version.

Abbreviation

TH: thyroid hormone; DIO: deiodinase; MCT: monocarboxylate transporter; OATP: organic anion-transporting polypeptide; LAT: L-type amino acid transporter; T4: thyroxine; T3: triiodothyronine; rT3: reverse T3; CNS: Central Nervous System; CH: Congenital hypothyroidism; TSRH: TSH releasing hormone; PAX: paired box; NKX: homebox protein; FOX: forkhead box; DUOX: dual oxidase; TG: thyroglobulin; TPO: thyroid peroxidase; SLC: solute carrier family; TRH: thyrotropin-releasing hormone; Pit-1: pituitary-specific transcription factor 1; TSH: thyroid-stimulating hormone; SCH: subclinical hypothyroidism; THR: thyroid hormone receptor; KO: knockout; BBB: blood brain barrier; CSF: cerebrospinal fluid; RXR: retinoid X receptor.

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