



# Hypothyroidism and Cognitive Disorders during Development and Adulthood: Implications in the Central Nervous System

Paulina Salazar<sup>1</sup> · Pedro Cisternas<sup>1</sup> · Milka Martinez<sup>1</sup> · Nivaldo C. Inestrosa<sup>1,2,3,4</sup> 

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## Abstract

Thyroid hormones (THs) play a critical function in fundamental signaling of the body regulating process such as metabolism of glucose and lipids, cell maturation and proliferation, and neurogenesis, to name just a few. THs trigger biological effects both by directly affecting gene expression through the interaction with nuclear receptors (genomic effects) and by activating protein kinases and/or ion channels (short-term effects). For years, a close relationship between the THs hormones and the central nervous system (CNS) has been described, not only for neuronal cells but also for glial development and differentiation. A deficit in thyroid hormones triiodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>) is observed in the hypothyroid condition, generated by a iodine deficiency or an autoimmune response of the body. In the hypothyroid condition, several cellular deregulation and alterations have been described in dendrite spine morphology, cell migration and proliferation, and impaired synaptic transmission in the hippocampus, among others. The aim of this review is to describe the role of the thyroid hormones with focus in brain function and neurodegenerative disorders.

**Keywords** Thyroid hormones · Brain function · Neurodegenerative disease

## Introduction

Thyroid hormones (TH) are crucial for multiple body functions, from development in prenatal stages, such as neural growth and differentiation, up to adulthood functions, like memory and concentration, maintenance of metabolic rate, equilibrium of reactive oxygen species (ROS), cardiovascular function, thermogenesis, and feeding [1, 2]. Also, in the last years, THs has been involved in more complex processes

including the regulation of some clock genes expression and memory/learning task [3].

A deficit in thyroid hormones triiodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>) is observed in the hypothyroid condition, produced mainly by an iodine deficiency or an autoimmune response of the body [4–7]. This condition affects 1–2% of the population, where the incidence increases 10 times more in women than in man, while in iodine-deficient areas, equivalent to one third of the world's population, the prevalence increases up to 80% [5]. The main locations affected by this problem are South Asia and sub-Saharan Africa. During pregnancy, the fetus relies on the mother's thyroid hormones until the 12–14 weeks of gestation [8]. Nowadays, hypothyroidism during pregnancy affects 2.5% of women, and congenital hypothyroidism has an incidence of one newborn in 3500–4000 births [5]. The impact of a deficiency during the development period has shown impaired growth and neurodevelopment; alterations in dendrite spine morphology, cell migration and proliferation; and impaired synaptic transmission in hippocampus has been detected [5, 9, 10]. Furthermore, a relationship between suboptimal thyroid function during pregnancy with low child intelligence quotient (IQ) and attention-deficit/hyperactivity disorder (ADHD) has been established [6].

Postnatal studies showing alterations in thyroid hormones have revealed perturbations in glucose metabolism,

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Paulina Salazar and Pedro Cisternas contributed equally to this work.

✉ Nivaldo C. Inestrosa  
ninnostrosa@bio.puc.cl

- <sup>1</sup> Centro de Envejecimiento y Regeneración (CARE UC), Departamento de Biología Celular, Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile, Santiago, Chile
- <sup>2</sup> Centre for Healthy Brain Ageing, School of Psychiatry, Faculty of Medicine, University of New South Wales, Sydney, Australia
- <sup>3</sup> Centro de Excelencia en Biomedicina de Magallanes (CEBIMA), Universidad de Magallanes, Punta Arenas, Chile
- <sup>4</sup> CARE UC Biomedical Research Center, Faculty of Biological Sciences, Pontificia Universidad Católica de Chile, Av. Bernardo O'Higgins 340, P. O. Box 114, -D Santiago, Chile

hypothalamus energy imbalance, and hippocampal structure and synaptic plasticity, affecting the general brain function [11, 12]. Adult neurodegenerative diseases has also been related with hypothyroidism, specifically both in Alzheimer's disease (AD) and Parkinson's disease, were a thyroid hormone imbalance has been reported in numerous cases [13]. Furthermore, several pathways or potential biomarkers involved in these diseases are related to thyroid hormone targets, but the specific relation is still unknown [14, 15]. The aim of this review is to understand the complexity of thyroid hormone actions with focus in neurodegenerative diseases from developmental stages up to senile stages.

## Mechanism of Action of Thyroid Hormones

Thyroid hormone action is influenced by several cellular mechanisms, from the amount of local ligand conversion, specialized membrane transporters, thyroid hormone receptor isoform, crosstalk with other key cellular pathways and nuclear corepressors and coactivators. This denotes the complex mechanisms that underlies the action of thyroid hormones [16–18].

At the cellular level, TH exerts an effect in the metabolism of proteins, carbohydrates, and lipids, affecting numerous processes, including metabolic pathways and growth and inflammatory processes [19]. The uptake of thyroid hormones by the cells is mediated through specific transporters that are expressed in different proportions and cell type depending on the developing stage. The main transporters in the brain are the monocarboxylate transporter (MCT), L-type amino acid transporters (SLC7), and the organic anion transporter polypeptides (OATPs) that may express differentially in oligodendrocyte, astrocyte, neurons, microglia, and endothelial cells [16, 20]. Once inside the cells, thyroid hormones generate their physiological actions through the interaction of T<sub>3</sub> with thyroid hormone nuclear receptors (TR), which exists in four isoforms, these are  $\alpha 1$ ,  $\beta 1$ ,  $\beta 2$ , and  $\beta 3$ . These nuclear receptors act as transcription factors that activates with the binding of T<sub>3</sub>, and as transcriptional repressors in the absence of this hormone [21, 22]. These thyroid hormone receptors are also expressed in different proportions in organs. TR $\alpha 1$  is predominantly expressed in the brain, heart, and skeletal muscle, while TR $\beta 1$  is expressed extensively; TR $\beta 2$  is expressed in the brain, retina, and inner ear and TR $\beta 3$  is expressed in kidney, liver, and lung [2]. Thyroid hormones have numerous target genes (Table 1), among them in the brain are *Reln*, which product, Reelin, acts as an extracellular matrix protein produced by neurons and which activity has effects in neuronal migration [23, 26]; *Nrgn* (RC3/neurogranin), a brain-specific protein kinase C (PKC) substrate, that has been implicated in the hippocampal plasticity process such as long-term potentiation (LTP) [32]; and *Shh*, a key developmental

morphogen, are some of the genes upregulated with T<sub>3</sub> treatment. There are also genes downregulated in rats were hypothyroidism was induced (Table 2), for instance, brain-derived neurotrophic factor (BDNF), which has been implicated in structural changes at synapses and *Laminin*, a guidance molecule in neuronal migration [33, 34].

Thyroid hormones have complex actions because of their impact in other signal transduction pathways and direct interaction with other nuclear receptors [36]. Within the metabolic pathways that are interconnected with the action of thyroid hormones are the retinoic acid and glucocorticoids during neural development. This was demonstrated through gene expression studies of key enzymes involved in the retinoic acid synthesis and degradation such as *Aldh1a3* and *Aldh1a1* that corresponds to the aldehyde dehydrogenase enzyme. Retinoic acid has a role in relevant processes such as sleep, learning, and memory, and also stimulates MCT8 expression and thyroid transport [37]. Both *Aldh1a3* and *Aldh1a1* were upregulated and downregulated by T<sub>3</sub>, respectively. This was related as well with a synergist effect of T<sub>3</sub> and dexamethasone (synthetic glucocorticoid), were the latter increases the expression of *Aldh1a1*. This was all in fine coordination with the subtype of the thyroid hormone receptor at a nuclear level [26]. Moreover, the *Klf9* gene, which mediates effects of glucocorticoids on neuronal structure and function, is also upregulated by thyroid hormone. Findings in the hippocampus and cerebellum demonstrate that this interaction occurs through a T<sub>3</sub> response element in the 5' flanking region of the *Klf9* gene [26, 29].

Further pathways involving thyroid hormones have been elucidated in other organs such as the liver, were thyroid hormone control cholesterol metabolism through the stimulation of low-density lipoprotein (LDL) receptor expression, the inhibition of the enzyme that degradates cholesterol to bile acids (CYP7A1), and through the crosstalk with proliferator peroxisome receptor (PPAR) elements [38]. These studies emphasize the complexity of thyroid hormone actions and the numerous crosstalk's that impact in different organs.

## Hypothyroidism

Hypothyroidism is a clinical condition in which the thyroid gland produces insufficient levels of the thyroid hormones T<sub>3</sub> and T<sub>4</sub>, leading to high thyroid stimulating hormone (TSH) values, and has a major consequence which is reflected in a slowdown of the cell metabolism. The causes of this condition are iodine deficiency (water, plants, and foods) and autoimmune disease caused by Hashimoto's thyroiditis or thyrotoxicosis caused by Graves's disease. The treatment of hypothyroidism is through the administration of levothyroxine, that together with the action of deiodinases of the body, T<sub>4</sub> will transform it to T<sub>3</sub>, were the latter is the hormone that produces

**Table 1** Thyroid hormone interaction with CNS genes

Gene upregulated by TH	Protein	Model	Function	References
<i>Reln</i>	Reelin	Rat	Neuronal migration	[23–25]
<i>Dio3</i>	Deiodinase, iodothyronine, type III	Primary cerebrocortical cells	Inactivation of thyroid hormone	[26]
<i>Aldh1a1</i>	Aldehyde dehydrogenase 1a1	Primary cerebrocortical cells	Enzyme that promotes the retinoic acid synthesis	[26, 27]
<i>Hr</i>	Hairless	Rat	Nuclear receptor corepressor of TR	[27, 28]
<i>Klf9</i>	Krüpfel-like transcription factor 9	Rat and mouse	Mediate effects of glucocorticoids on neuronal structure and function	[29, 30]
<i>Shh</i>	Sonic hedgehog	Rat and primary cerebrocortical cells	Developmental morphogen	[26, 31]

the main effect at a transcriptional level. This therapy is capable of regulating the TSH levels to the stipulated “normal values.” Nevertheless, a subgroup of patients still presents symptoms of hypothyroidism [38–40]. Hypothyroidism may be triggered in all the stages of development, from pregnancy as subclinical hypothyroidism and congenital hypothyroidism, in which the latter have a greater impact in neurodevelopment retardation and metabolic impairments such as poor feeding and failure in weight gain and growth, up to adulthood where even the subclinical hypothyroidism has been related to depression and dementia [41–43]. Thyroid hormones are implicated in metabolic alterations in several organs, where the brain is fundamental.

### Hypothyroidism during Development

The effect of a deficiency in thyroid hormones depends on the stage in which is presented; for instance, congenital hypothyroidism can produce impairment of growth and development of the skeletal system, while if it is presented in childhood it could cause poor visuomotor and visuospatial abilities, delayed speech and language development, neuromotor deficiencies, and poor attention and memory skills. In telencephalon, studies have revealed that maternal hypothyroidism during pregnancy leads to an inhibition in neurogenesis and impairments in learning and memory. Furthermore, specifically in the hippocampus, when analyzing structural and growth properties in this region from an early postnatal hypothyroid condition, a significant reduction was found in the surface of

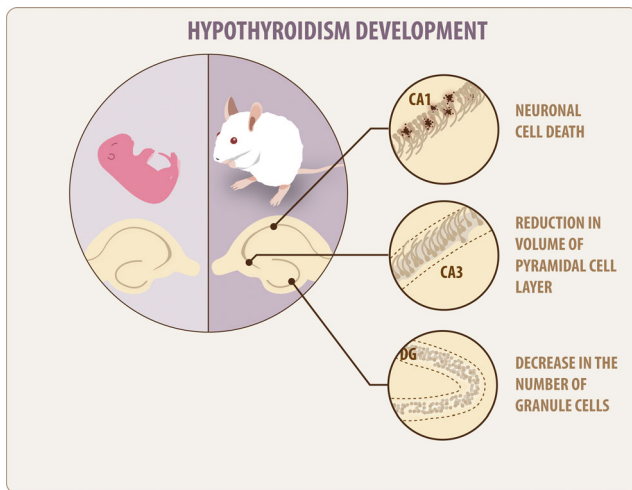
the hippocampus, being CA1 the more affected region [44]. Also, studies in early postnatal rat development found that the number of granule cells of the dentate gyrus of the hippocampus is diminished in hypothyroid animals, while in the CA1 region occurs an irreversible neuronal cell death after postnatal hypothyroidism induction. In the CA3 region, there is a reduction of the volume of the pyramidal cell layer, but not in the number of these (Fig. 1) [45, 46].

The most common method for analyzing the effect in developing animals is by the administration of propylthiouracil (PTU) to pregnant rats and lactating dams through the water. Studies in target genes of thyroid hormones have been made in rat development exposed to PTU, specifically in the regions of the cerebral cortex, corpus callosum, dentate gyrus, and cerebellar vermis. All these areas showed changes in genes involved in neuronal differentiation, development, cell migration, synaptic function, and axonogenesis. Alterations in genes of the ephrin signaling and the ionotropic glutamate receptor AMPA were observed, which are involved in neuronal migration. Furthermore, genes encoding cyclooxygenase 2 (COX2) were downregulated in the hippocampal dentate gyrus, which has been related with neurogenesis [47, 48]. Moreover, studies in vitro revealed that T<sub>3</sub> promotes the neuronal differentiation of mouse embryonic neural stem cells. The action was through the inhibition by TR $\alpha$ 1 over the JAK/STAT3 signaling activity. The final effect contributes to early neurogenesis in the embryonic telencephalon [49].

Functional properties of the hippocampus observed through electrophysiology have also been addressed. Studies

**Table 2** Hypothyroidism alterations of genes in the CNS

Gene downregulated by hypothyroidism	Protein	Model	Function	References
<i>Laminin</i>	Laminin	Rat	Guidance molecule in neuronal migration	[33, 34]
<i>Arc</i>	Activity-regulated cytoskeletal protein	Rat	Synaptic plasticity	[30, 35]
<i>Bdnf</i>	Brain-derived neurotrophic factor	Rat	Structural changes at the synapse	[30, 35]
<i>Homer-1</i>	Homer homolog 1	Rat	Scaffold protein that associate with glutamatergic receptor	[27, 35]
<i>Nrgn</i>	RC3/neurogranin	Rat	Synaptic plasticity	[32]



**Fig. 1** Hypothyroidism during hippocampus development. Hypothyroidism in the early postnatal stage triggers in the hippocampus structural and growth defects, such as irreversible neuronal death in the CA1 region, decrease of the volume of pyramidal cell layer in CA3, and a decrease in the number of granule cells in the dentate gyrus

have shown reductions in synaptic transmission and impairment of short-term synaptic plasticity and LTP in the dentate gyrus electrophysiological recordings. The Morris Water Maze task revealed impairment in spatial learning that was dependent of the PTU dose. Also, thyroid hormone insufficiency during late gestational periods has shown permanent alterations in synaptic transmission and plasticity in adult animals in this area [50, 51]. In CA1 recordings, paired pulse inhibition of the population spike is also reduced, but in contrast, LTP magnitude was increased; this is supported by the fact that the phosphorylation of the extracellular signal-regulated kinases was increased. These alterations are hypothesized to be due to differential expression or localization of N-methyl-D-aspartate (NMDA) receptors and voltage-dependent calcium channels (VDCC) on pyramidal cell soma versus dendrites triggered by an early thyroid hormone insufficiency [52].

Also, the administration of low doses of PTU, in the drinking water, from gestational (day 14) to early postnatal ages (21 days) is enough to induce a middle impair in cognitive performance in males. These results were correlated with a decrease in the expression of some neurotransmitters such as glutamate and glycine in the hippocampus. Additionally, a decrease in the expression of N-methyl-D-aspartate receptor subunits, which play a role in the neurotransmission related with the cognitive performance in the hippocampus was observed [53]. Also, the induction of hypothyroidism during pregnancy induces changes in the DNA hypermethylation of some important genes for brain function such as brain-derived neurotrophic factor gene (*Bdnf*), which is critical for several brain functions including the neuroplasticity related with the process of memory and learning in the hippocampus [54].

The levels of thyroid hormones are critical in all stages; for instance, in hypothyroidism induced during early postnatal stages, several changes in the brain function has been described, including decreases in the cognitive performance and LTP, along with an increase in several markers for oxidative stress such as 4-hydroxy-2-nonenal [55]. Together, all these results confirm the importance of thyroid hormones for brain function in several ages; however, the target for these effects has not been completely studied.

### Relationship between Hypothyroidism and Metabolism

Thyroid hormones are crucial for the functioning of almost all organs, and a deregulation in the levels of TH has been described to impact the cardiovascular system, adipose tissue, liver control of glucose levels, growth process, fertility, and the CNS [21, 56–58]. For instance, a study in young rats demonstrates that in a dose-dependent manner, PTU has a negative effect on body and organ weights, where kidney and heart decreases their weight, while the testes, brain, and thyroid gland increases [59].

Taking into consideration that glucose is one of the main supply of energy of the body, the regulation and maintenance of glycemic levels is essential for the correct functioning of the organism. THs have a role in the regulation of carbohydrates, and it has been reported that hypothyroidism can reduced the glucose availability, alter the correct absorption of glucose, and delay gluconeogenesis, reducing insulin synthesis. In fact, hypothyroidism has been associated with metabolic diseases, such as diabetes, were thyroid dysfunction has been found in up to an 11% of diabetic patients [56]. Considering that glucose is the main supply of the brain, and cognitive performance depends on it, an energy imbalance may affect major functions in the brain. Studies with PET in patients with hypothyroidism has shown a reduction in brain regional activity, specifically in the bilateral amygdala, hippocampus, perigenual anterior cingulate cortex (ACC), left sub-genual ACC, and right posterior cingulate cortex [60]. These regions are essential for emotions, incorporation of attentional information, and memory [61, 62]. Regardless of the imbalance in the levels of thyroid hormones, whether it is a decrease or excess of hormones, the glucose metabolism in the brain is diminished. Patients with hyperthyroidism also present a deregulation in cerebral glucose metabolism, where lower levels have been detected in the limbic system, frontal lobes, and temporal lobes. Improvements after thyroid hormone treatments were observed in memory and constructive abilities; nevertheless, not all of the brain regions return to normal activity levels; this could be due to mood disorders for instance; therefore, further studies to reach an optimal conditions are needed [63]. Moreover, a study in which the glucose transporter 1 (GLUT1) was analyzed in hypo-hyperthyroid rats in

different age conditions showed decreased levels in the expression of this transporter in both conditions in young rats, while it was increased in hyperthyroid aged rats; therefore, age condition in glucose metabolism must be considered as well. Mice with primary hypothyroidism in early postnatal stages also showed a decline in GLUT1, while GLUT3 has no changes, and hexokinase enzyme activity was enhanced by a compensatory mechanism [64, 65].

Adult cognitive functions are also imbalanced in hypothyroid conditions. The hippocampus is a region of the brain where neurogenesis occurs, a process that has an important role in learning and memory [66]. Studies with TR $\alpha$ 1 and TR $\alpha$ 2 knockouts reveal a key role of TR $\alpha$ 1 in the regulation of the survival of adult hippocampal progenitors, indicating that a deficiency in this nuclear receptor enhances hippocampal progenitor survival; this has been explained by the possible role of TR $\alpha$ 1 in regulating commitment and maturation of neuronal progenitors [67, 68].

Another relevant area has been investigated, this is the hypothalamus, where a deregulation of thyroid hormones leads to energy imbalance in thermogenesis. A model with a mutation in TR $\alpha$ 1 presents a hypermetabolic state with increased thermogenesis and energy expenditure. This has direct effects in the weight of the animals, demonstrated by the fact that a high-fat diet (HFD) did not normalize the body weight; therefore, the central effect of thyroid hormones overrides the peripheral effects [12, 69]. Furthermore, there is evidence of the pathways involved in the regulation of this energy balance, where energy expenditure is controlled via AMP kinase and feeding with the mTOR pathway [70].

In addition, diabetes mellitus (DM), a highly prevalent and complex metabolic disorder in modern societies worldwide, has been associated with higher risk of cognitive impairments, dementia, and other behavioral/neurological changes [71]. These alterations have been associated with an increase in the levels of insulin but correlated with an increase in the insulin resistance. In fact, diabetic rats induced by alloxan present hypothyroidism and increased expression of proinflammatory cytokines, which are known to reduce insulin sensitivity [72]. In diabetic rats treated with T<sub>3</sub> for 4 weeks was observed a recover of the insulin signaling and the glucose levels [73].

## Relationship of Hypothyroidism with Brain Disorders

As previously described, hypothyroidism affects several brain functions during development and adulthood, therefore impairs a great number of pathways in diseases such as congenital hypothyroidism and autism in childhood, but also in elderly diseases such as Parkinson's and Alzheimer's diseases (Fig. 2) [74–76].

## Autism and Thyroid Dysfunction

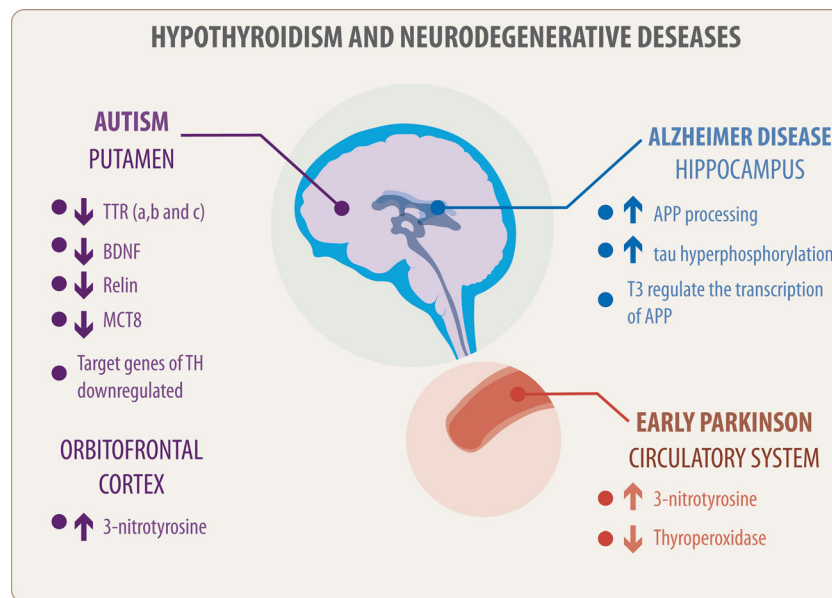
Nowadays, the idea of a relationship between thyroid hormone deregulation and autism spectrum disorders (ASD) is gaining force. ASD includes autism and Asperger's syndrome, and these are neurobiological disorders with a developmental disturbance of communication that impairs social interaction and communication. It affects 1 in 132 persons, with a higher prevalence in males. The degree of severity of the symptoms may vary, from intellectual and language disability up to epilepsy. The specific cause of this disorder is yet unknown, but it has a genetic component, and also it is thought that a combination of genes with the environment may contribute to the severity of this disorder [77]. Considering that human thyroid hormones are essential for brain development, an impairment of TH during pregnancy has been associated with autism. Evidence shows association between family history of hypothyroidism with an increase in the risk of childhood autism, with a higher risk in children with maternal hypothyroidism. More specifically, a postmortem study of patients with ASD was conducted to analyze thyroid hormones target genes. Results showed a brain region-specific disruption of TH and gene expression in autism, specifically in the putamen, a region that influences reinforcement and implicit learning, the levels of genes such as TTR (a, b, and c), BDNF, RELN, and MCT8 where downregulated [78–80]. Interestingly, the levels of T<sub>3</sub> were decreased and the oxidative stress marker, 3-nitrotyrosine (3-NT), was increased in the orbitofrontal cortex area in male patients with ASD (Fig. 2).

A Danish nationwide study revealed increased risk of ASD when the mother presented hypothyroidism during pregnancy, and a Rotterdam study showed a fourfold increase in the risk of autism in children with maternal hypothyroxinemia [76, 81]. Furthermore, autoimmune disease has been associated with ASD, through the measure of maternal TPO-Ab antibody. Specifically, autoimmune thyroid disease has been associated with ASD that presented regression, a phenomenon where established skills in communication or social interaction are lost [82, 83].

## Parkinson's Disease and Hypothyroidism

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease presented mainly in later years of life, characterized by impaired motor function, slow movement, tremor, and postural instability, among others. Different causes have been associated to this disease, such as psychiatric disorders, socioeconomic status, autoimmune disease, and hormone dysfunctions [84, 85].

Parkinson's disease and hypothyroidism are two disorders that are common in the elderly population, and they share many clinical characteristics. In the past, several studies has



**Fig. 2** Hypothyroidism and neurodegenerative diseases. Hypothyroidism is related to several neurodegenerative diseases, among them are autism, AD, and Parkinson's disease. In autism, specifically in the putamen region, a reduction in thyroid hormone target genes are downregulated, such as TTRa, TTRb, TTRc, BDNF, Relin, and MCT8, while in the orbitofrontal cortex occurs an increase in the oxidative stress marker 3-nitrotyrosine. In AD patients, the levels of  $rT_3$  and  $rT_3/T_4$  are increased in

the cerebrospinal fluid. Moreover, a negative regulation of  $T_3$  over the transcriptional activity of APP has been observed, along with an increase of the processing in APP, therefore  $A\beta$  amount increases. Also, tau hyperphosphorylation, the neuropathological marker of AD, increases in rats with hypothyroidism. Finally, in early Parkinson's disease, the increase of 3-nitrotyrosine correlates with a decrease in thyroperoxidase

found a relationship between hypothyroidism and PD, for instance Berger and Kelley [86] reported that hypothyroidism has a 6.6% of incidence among Parkinson's patients, but in the recent years no significant difference has been found between control and PD patients regarding to hypothyroidism, except for a nationwide epidemiological study from Sweden with 310,000 patients, were among the autoimmune disease as a risk factor for PD, Hashimoto's disease/hypothyroidism is one of them [75]. In PD, several clinical biomarkers have been proposed to detect this disease in early stages, where one of them is the presence of the oxidative marker 3-NT in serum in early Parkinsonian patients. In relation with thyroid hormones, one study described an increase of the enzyme thyroperoxidase that was negatively correlated with serum 3-nitrotyrosine protein in patients with early Parkinson's disease (Fig. 2); therefore, they propose a possible role of the thyroid gland and thyroperoxidase in the nitrosylation of serum proteins, thus influencing Parkinsonian nitrosative stress [87].

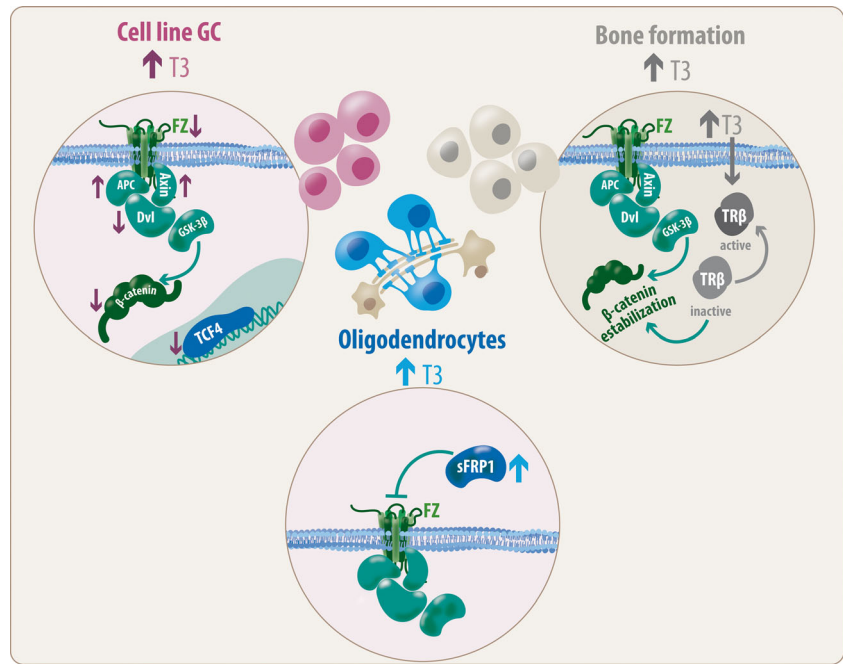
### Hypothyroidism and Alzheimer's Disease

Nowadays the population aging is advancing, and dementia affects more than 25 million people worldwide were Alzheimer's disease (AD), a neurodegenerative disease, is the most common form of dementia, having an incidence in people over 65 of about 20 per 1000 person-year and 15 per 1000 in Europe and the USA, respectively. The amount of people affected increases almost exponentially when the age

is above 85. AD is still a disease without any medical treatment, which clinically is diagnosed once the pathology has already began [88]. It is characterized by a decline in cognitive functions and physical disability, leading to institutionalization and a deterioration in quality of life. Different factors may impact in the development of the disease, such as genetic, vascular, psychosocial, and dietary, among others. Neuropathologically, it is characterized by the presence of aggregated amyloid protein, tau hyperphosphorylation, increased reactive oxygen species, and decreased glucose consumption [88–91].

In the last years, thyroid hormone imbalance in AD has been addressed as another factor to consider in this pathology, considering that both diseases increase their prevalence with age. Thyroid hormone levels in the cerebrospinal fluid from diagnosed AD patients revealed increased  $rT_3$  levels and increased  $rT_3$  to  $T_4$  ratio, regardless the euthyroid systemic condition when these hormones were measured in serum. This is in accordance with findings of an association between AD and abnormal function of the hypothalamic-pituitary thyroid axis. This is fundamental when considering that  $T_3$  negatively regulates the transcriptional activity of the  $\beta$ -amyloid precursor protein gene (APP), an important risk factor of AD. This was observed in human neuroblastoma cells and in primary cultures of rat neurons. Further studies revealed that hypothyroidism induced the amyloidogenic pathway, increasing the amount of  $A\beta$  peptides in the hippocampus. In addition, high

**Fig. 3** Relation between thyroid hormones and the Wnt pathway. Several components of the Wnt pathway are modulated by T<sub>3</sub> availability. In the GC cell line, the stimulation with T<sub>3</sub> triggers a decreased in Fzsd, Dvl, β-catenin, and TCF4, while an increase of APC and Axin is produced. In bone formation, the Wnt pathway is normally activated because of the stabilization of β-catenin by TRβ. Contrary, T<sub>3</sub> treatment inhibits this pathway, most likely through the competition for TRβ. In oligodendrocytes, the stimulation with T<sub>3</sub>, produced an increase of the endogenous inhibitor of the Wnt pathway, sFRP1



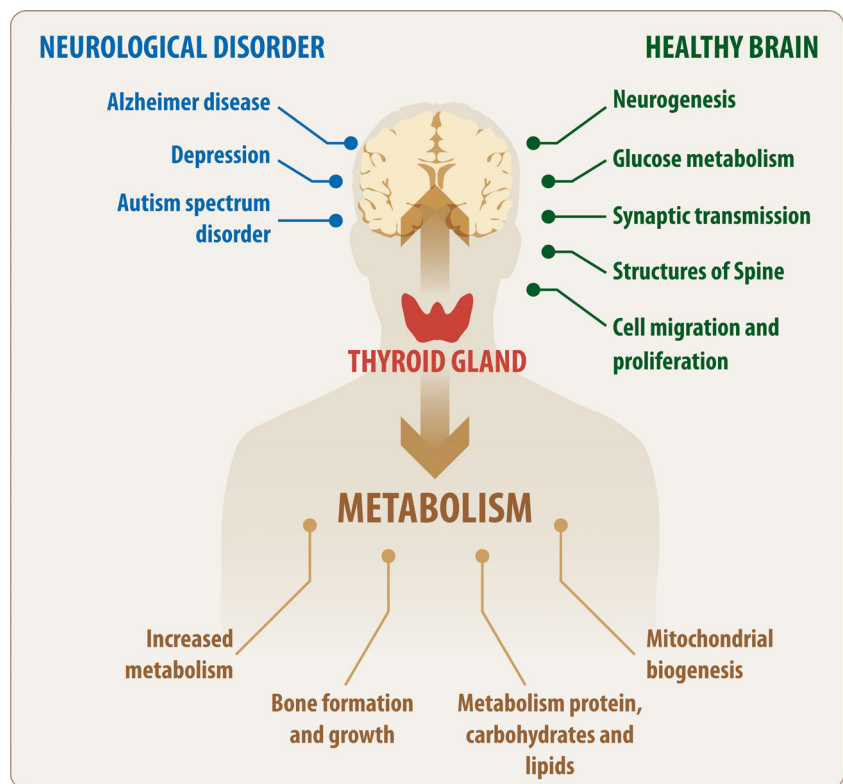
and low levels of TSH have been associated with increased risk of developing AD in women (Fig. 2) [74, 92–95].

Further studies in adult rats with hypothyroidism revealed that several neuropathological signs of Alzheimer were present, such as tau hyperphosphorylation in the hippocampus, increased levels of proinflammatory cytokines, and altered expression of signaling molecules implicated with synaptic

plasticity and memory. In addition, spatial memory was impaired [14].

In AD, several studies have revealed a deregulation in molecular pathways, where the Wnt pathway has gained force in the last years [96, 97]. The Wnt pathway is activated by Wnt ligands and exerts an effect in many cellular processes during embryonic development, such as cell proliferation, cell

**Fig. 4** Effects of thyroid hormones in normal and pathologic conditions. The thyroid gland is in charge of thyroid hormone production, which impacts the general metabolism in aspects such as bone formation, growth, carbohydrates, and lipid metabolism. Also, in normal conditions, controls brain process, such as neurogenesis, synaptic transmission, synaptic structure, cellular proliferation and migration, and glucose metabolism (in this case, the thyroid hormones could affect several parameters including expression of glucose transporters, enzyme activities, and mitochondrial biogenesis). Nevertheless, these hormones are also involved in neurological disorders, such as AD, depression, and autism spectrum disorders, among others



polarity, cell migration, and neural patterning and also influences adult homeostasis. This pathway may be classified as a canonical (Wnt/ $\beta$ -catenin) or non-canonical pathway, where the first one regulates the amount of  $\beta$ -catenin, a protein that functions as a transcriptional co-activator of gene expression of the T cell factor/lymphoid enhancer factor (TCF/LEF) [98, 99]. Normally, the  $\beta$ -catenin protein is being degraded by a destruction complex, in which one of the proteins, the glycogen synthase kinase 3 (GSK3), is constantly phosphorylating  $\beta$ -catenin, leading to its proteasomal degradation in the cytoplasm and therefore preventing to reach the nucleus. When a Wnt ligand binds to a Frizzled receptor and its co-receptor, it activates the Wnt pathway and inhibits the phosphorylation of  $\beta$ -catenin, with the consequent activation of gene expression. The non-canonical Wnt pathway is divided into the Planar Cell Polarity pathway (PCP) and the Wnt/ $\text{Ca}^{+2}$  pathway. The PCP pathway activates the small GTPases Rho and Rac that activates other pathways related to actin polymerization. The Wnt/ $\text{Ca}^{+2}$  pathway depends on G proteins that activates the enzyme phospholipase C, with the consequent production of diacylglycerol and inositol triphosphate (IP3). IP3 is capable of stimulate the intracellular  $\text{Ca}^{+2}$  release from the ER, that in turn activates proteins sensitive to  $\text{Ca}^{+2}$ , such as protein kinase C (PKC) and calcium/calmodulin-dependent kinase II (CamKII) and calcineurin [100–102]. Considering that both the Wnt pathway and thyroid hormones has as targets the expression of genes, a possible interaction of these two pathways has been proposed.

### Wnt and Thyroid Hormones Relation

Currently, the evidence of an interaction between thyroid hormones and the Wnt pathway is validated by several studies in tissues and cell lines. In thyroid cell line, Pax8, a gene involved in morphogenesis of the thyroid gland was found to modulate the expression of Wnt4 at a transcriptional level, through the direct binding of the promotor of Wnt4, and the consequent activation of the expression of this pathway [103, 104].

The regulation that thyroid hormones has over the Wnt pathway has been studied to analyze the temporal expression of these genes. A study that uses the cell line GC, that expresses functional thyroid hormone receptors (TRs), revealed through microarray that  $\text{T}_3$  proliferation induction repressed the expression of key regulators of the Wnt pathway and inhibits transcriptional elements of the  $\beta$ -catenin/TCF complex. Specifically, the following components were downregulated:  $\beta$ -catenin, TCF4, Dishevelled-1, Frizzled, and c-jun. In accordance, the expression of axin and APC (repressors of the Wnt pathway) were increased (Fig. 3) [105].

Thyroid hormones have a role in bone formation during growth and Wnt canonical signaling has also been implicated in this process. During this process, the Wnt pathway is

activated, increasing bone mass through the stimulation of osteoblastic bone formation, most likely due to physical interaction between TR $\beta$  and  $\beta$ -catenin, that stabilizes  $\beta$ -catenin. In contrast,  $\text{T}_3$  treatment inhibited the Wnt signaling due to the competition of the binding to the receptor. Studies in transgenic mice *Thrb*<sup>PV/PV</sup>, characterized by an impaired pituitary-thyroid axis and high levels of thyroid hormones, in which the mice developed thyroid carcinogenesis, revealed that  $\text{T}_3$  failed in the inhibition of the Wnt pathway [106, 107]. Furthermore, the induction of hyper- or hypothyroidism correlated with this results, while the hyperthyroid condition produces an increase in bone formation that correlated with low levels of DKK1; the contrary occurred with the hypothyroid condition (Fig. 3) [108]. Studies in hepatocytes has also demonstrate the role of  $\text{T}_3$  over the Wnt pathway through the modulation of other genes; for instance,  $\text{T}_3$  union to the thyroid receptor activates the transcription of *Klf9*, and both transcription factors modulate pathways such as Notch, FGF (AD amyloid secretase pathway), TGF $\beta$ , and the Wnt pathways [109]. Since *Klf9* is a relevant gene in the modulation of neurogenesis and glucocorticoids in brain, the interaction of  $\text{T}_3$ -*Klf9*-Wnt could be an interesting pathway to study in the CNS.

There are few studies in CNS that relates Wnt with thyroid hormones. Among these, experiments in oligodendrocyte progenitor cells treated with  $\text{T}_3$  hormone showed an increase in secreted Frizzled-related protein-1 (SFRP1), an inhibitor of the Wnt pathway [110].

### Conclusions

Thyroid hormones are critical for the correct brain function, modulating critical roles including neurogenesis, cognitive performance, and energy brain metabolism (Fig. 4). The blood levels of  $\text{T}_3$  and  $\text{T}_4$  are regulated by several mechanisms that involve the participation of several tissues. However, for several conditions including genetic patterns or environment interaction, a decrease in blood levels of thyroid hormones may be the trigger, causing a wide deregulation downstream. When this hypothyroidism is established in the early stages of development, it produces brain alterations that could affect patients even in adult stages. Until now, several reports has correlated the function of thyroid hormones with several neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease and autism. Nevertheless, little is known about the specific cellular mechanism that could be altered by the dysfunction induced by the decrease in thyroid hormone levels. Therefore, it is important to develop efficient tools against the consequences of hypothyroidism in early stages of life and in this manner prevent some brain pathologies in the adulthood.



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## Compliance with Ethical Standards

**Conflicts of Interest** The authors declare that they have no conflict of interest.

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