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Implication of Thyroid Hormones in the Development of the Pathological Characteristics of Alzheimer's Disease; A Mini Review

Carrera-González MP* and Cantón Habas V
Department of Nursing, Reina Sofía University Hospital, Spain

***Corresponding author:** Carrera Gonzalez MP, Department of Nursing, Faculty of Medicine and Nursing, Institute of Biomedical Research of Córdoba (IMIBIC) IMIBIC Building, Reina Sofía University Hospital, Av. Menéndez Pidal, 7, 14004 Córdoba, Spain

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Abstract

Thyroid hormones play key roles in the central nervous system. Indeed, thyroid dysfunctions, either in the form of hypothyroidism or hyperthyroidism, have been recognized as risk factors for the progression of irreversible dementia, suggested by the epidemiological findings, being hypothyroidism is a condition that becomes more prevalent with age. The aging of the population is leading to the appearance of neurodegenerative diseases such as Alzheimer's disease. Alzheimer's disease is a multifactorial neurodegenerative disease which occurs relatively later in life (onset > 65 years of age, 95% of cases.). It involves a combination of aggregated proteins, chronic neuroinflammation and neuronal cell loss. Several studies have identified an association between dysregulation of thyroid hormones and Alzheimer's disease dementia.

The aim of this review is to determine the involvement of thyroid hormones in the different hallkmarks that characterize Alzheimer's disease.

Keywords: Thyroid hormone; Hypothyroidism; Alzheimer disease; Amyloid plaques

Introduction

The most widely identified association between endocrine and cognitive functions involves Thyroid Hormones (THs) [1]. Although the increase in longevity in western populations is our main achievement, it is a challenge for socioeconomic sustainability and a burden for health care systems since we are facing age-related diseases, as is the case of Alzheimer's disease [2]. In this sense, TH dysregulation in advanced age is associated with risk for dementia [3-6]. Indeed, hypothyroidism is a condition that becomes more prevalent with age. Patients with untreated hypothyroidism have consistently reported symptoms of severe cognitive impairments. In patients suffering hypothyroidism, thyroid hormone supplementation offers the prospect to alleviate the cognitive consequences of hypothyroidism. However, the link between cellular modifications associated with hypothyroidism and neurodegeneration remains to be elucidated [7]. Thereby, T3 supplementation can alleviate hippocampal-dependent memory impairments displayed by hypothyroid rats and normalize key markers of thyroid status in the hippocampus, of neuroinflammation, Aβ production, and of cell-signaling pathways known to be involved in synaptic plasticity and memory function [7]. On the other hand, the literature indicates a complicated relationship between TH and dementia risk so hyperthyroidism is usually more strongly associated with cognitive decline, although some reports indicate that hypothyroidism also is a risk factor for dementia [8-12].

Therefore, AD appears to lie on an intricate crosstalk between age-related metabolic, hormonal and specific genetic changes that challenge its traditional view [13].

THs have been implicated in practically all clinical features of AD. However, the mechanism underlying such involvement is unknown. In this review, we intend to describe the aforementioned relationship.

Alzheimer disease

Alzheimer's Disease (AD) is the leading cause of dementia [14], affecting ~35 million people worldwide [15], ~2/3 of them are women [16]. Clinically, AD is a progressive neurodegenerative disease that typically begins with a subtle decline in the ability to encode new memories, then progressing towards a more profound cognitive, behavioural/personality and adaptive deterioration [17,18]. In this sense, there is evidence that TH regulates two of the main pathogenetic processes in AD, namely, tau protein phosphorylation [19] and the altered metabolism of amyloid precursor protein [20].

Classic hallmark characteristics of AD pathology include Aβ plaques and oligomers, tau neurofibrillary tangles and progressive cholinergic neuron degeneration [21]. Also, proliferation and activation of microglia in the brain, concentrated around amyloid plaques, is a prominent feature of AD [22].

Amyloid Precursor Protein (app) processing and thyroid hormones

Extracellular senile plaques arises from the amyloidogenic proteolytic processing of Amyloid Precursor Protein (APP), sequentially catalysed by the aspartic protease β-site APP Cleaving Enzyme-1 (β-secretase or BACE1) and then by the γ-secretase complex [17,23,24]. Several studies have indicated that THs regulate the gene expression of APP [25,26]. Belandia et al. [27] reported that T3 negatively regulates APP gene expression in a rat neuroblastoma cell line. The results of various studies suggest that decrease in TH receptor levels occur in Alzheimer hippocampus cells. Moreover, the

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effects of estradiol or retinoic acid on APP expression and metabolism suggested that members of the nuclear superfamily of receptors and their ligands might play the main role in AD [27]. In this context, it has been suggested that low CNS TH levels may predispose to AD via increasing APP expression and consequently, Aβ peptide and β-amyloid levels [1]. Indeed, preclinical studies have repeatedly found an association between thyroid hormones and brain Aβ deposition in mice [28-30] and in human brain-derived neuroblastoma cells [30].

In the last years different authors found that Aβ impairs hormone-mediated signalling, mitochondrial (energy) metabolism and calcium homeostasis, leading to oxidative/endoplasmic reticulum stresses, microglia activation/inflammation and endotelial dysfunction, culminating in synaptic/neuronal loss and cognitive deficits [31]. In this sense, there is evidence that TH regulates the altered metabolism of APP [20]. In addition, hypothyroidism interferes in the maintenance of normal energy (glucose)-consuming processes needed for essential brain functions such as neurotransmission and memory [32], harming cognition.

Recent evidence suggests that microglia form a protective barrier around amyloid deposits, compacting amyloid fibrils into a tightly packed and potentially less toxic form, preventing the accretion of new Aβ onto existing plaques, and reducing axonal dystrophy in the nearby neuropil [33]. On the other hand, there is also evidence that activated microglia can be harmful to neurons [22]. Proliferation and activation of microglia in the brain, concentrated around amyloid plaques, is a prominent feature of Alzheimer's Disease (AD). There is mounting evidence that microglia protect against the incidence of AD, as impaired microglial activities and altered microglial responses to β-amyloid are associated with increased AD risk [22]. However, we have not found detailed studies of the possible involvement of thyroid hormones in the process of activating microglia in AD, although its relevance in relation to amyloid plaques is definitive [1].

Tau protein phosphorylation and thyroid hormones

AD is determined pathologically by alterations in the brain including the formation of intracellular neurofibrillary tangles of hyperphosphorylated Tau [1]. Tau is an essential protein from the family of Microtubule-Associated Proteins (MAPs) that physiologically interacts with tubulin [34] to maintain axonal diameter [35] and microtubule stability [29,34,36-38], thus maintaining neuronal structure and axonal transport of synaptic vesicles [39]. However, P-Tau tends to aggregate within neuronal perikaryal, interfering with microtubule network, promoting oxidative stress, mitocondrial dysfunction, neurodegeneration and death [24,39]. Strikingly, Aβ may also induce P-Tau, exacerbating neurodegeneration/ neuronal loss and brain atrophy in AD [24,31].

In this context, THs could affect the transcription of APP gene as well as the phosphorylation of Tau [27,28,30,40,41]. Indeed, THs may also interact with the amount and phosphorylation of Tau [41,42], however, the mechanism involved is still unknown.

Cholinergic disfuction and thyroid hormones

The cortical cholinergic dysfunction begins in midlife and is closely followed by increases in deposition of cortical Aβ levels [43-45]. In neocortex and hippocampus of AD brain, a harm of cholinergic fibers and terminals, declines in cholinergic receptors and signal transduction, and significant decreases in choline acetyltransferase and increase in acetylcholinesterase enzyme activities have been reported [46,47].

The thyroid function has a central role in both neurodevelopment process and neurodegenerative processes. So it has been proposed that the thyroid dysfunction enhances the risk of AD by a direct harmful effect of thyroxine discharge on cholinergic neurons; however, whether the neuropathological mechanism of altered thyrotropin levels happens before or after the beginning of AD is unclear [48].

Bavarsad et al. [1] suggests a relationship between hypothyroidism and AD; reduced thyroxin level is associated with the preservation of cholinergic neurons [48], concentrations of lower T3 in the brain increase the expression of APP [30], and the TH receptor competitively increases the level of the seladin-1 gene which prevents the accumulation of β-amyloid plaques and cell death [49].

Therefore, thyroid dysfunctions, either in the form of hypothyroidism or hyperthyroidism, have been recognized as risk factors for the progression of irreversible dementia as suggested by the epidemiological findings [50,51]. In this sense, several reports suggest that subclinical abnormalities in thyroid function may play a role in AD [52-54].

Recent studies developed by Quinlan et al. [55], showed that serum FT3 levels were inversely associated with the risk of progression to AD, with a more than doubled risk of subsequent AD in the lowest FT3 quartile compared to the highest quartile. However there was no association between serum FT3 and all-cause dementia or vascular dementia, and serum levels of TSH and FT4 did not associate with the risk of conversion to dementia of any type. In this sense, authors suggest that supplementation with THs could be of use in patients with prodromal AD.

Conclusion

In view of the collected studies we can conclude that the alteration of thyroid hormones is involved in the development of Alzheimer's disease. In fact, they seem to be implicated in the processes underlying the appearance of hallmarks of Alzheimer's disease. However, based on current lack of knowledge of the specific pathophysiological mechanisms of Alzheimer's disease, as well as the involvement of thyroid hormones in the related cerebral metabolic pathways, a greater number of studies are needed in our view to delve into each one of these points.

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