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Dysthyroidism And Alzheimer's Disease: A Link Is Not As Rare As Previously Thought

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Abstract:
Alzheimer disease (AD) is the most common form of dementia, which is the fifth leading cause of death. AD can hinder the ability of an individual to perform everyday tasks, along with several aspects of daily life. Despite decades of research ,only a few causal risk factors have been identified, and those that have been identified are mostly non-modifiable.
Levels of thyroid hormones are thought to impact the risk of developing dementia. Thyroid hormones are known for their involvement in brain development; they influence adult neurogenesis. Many studies have investigated the association between thyroid function and dementia and demonstrated that clinical hypothyroidism, thyroiditis, and hyperthyroidism were significantly associated with AD, although the biological mechanisms remain unclear. Furthermore, some publications argue that there may be a role for the treatment of these thyroid diseases in the prevention of the development or progression of AD. Further research is warranted to elucidate causality and the directions of these associations.
Keywords: *dementia, Alzheimer's disease, thyroid function.*

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I. Introduction

Over the last century, scientific advances, particularly in medicine, have considerably increased life expectancy in industrialized countries. The aging of the population is often accompanied by associated diseases, such as dementia, which represent a major health problem in the 21st century. Alzheimer's disease (AD), the most common dementia affecting the elderly, has now become a public health priority. AD is a multifactorial neurodegenerative pathology that manifests itself, among other things, in memory impairment, executive function disorders, and difficulties with orientation in time and space. Patients progressively lose their cognitive faculties and autonomy. Research over the last century has identified two characteristic lesions: amyloid plaques and neurofibrillary degeneration. These two types of lesions are each associated with a protein compound: β-amyloid peptide for amyloid plaques and hyperphosphorylated Tau protein for neurofibrillary degeneration. Our understanding of the mechanisms involved in AD has evolved dramatically in recent years, and this progress has led to some very promising therapeutic strategies. However, despite considerable efforts in this direction, there is currently no cure, and the only existing treatments aim to slow the progression of symptoms. Given the scale of this public health problem, a preventive approach that complements the development of new therapeutic approaches is becoming an absolute priority. This preventive approach is based on two complementary approaches: The search for reliable biomarkers enabling early diagnosis of the disease and the development of animal models incorporating risk factors. These should contribute not only to the development of preventive approaches but also to the definition of new molecular pathways whose targeting could delay or even reduce the progression of the disease. Epidemiological studies suggest that lifelong exposure to various risk factors, such as intellectual and physical inactivity, diabetes, hypertension, hyperlipidemia, or cardiovascular disorders, may influence the onset of the disease. Recent data in the literature suggests that hypothyroidism, whose prevalence increases with age, may also be a risk factor for AD.

II. Pathophysiology of Alzheimer's disease

Alzheimer's disease is characterized neuropathologically by specific pathophysiological markers: senile plaques and neurofibrillary degeneration (NFD). These characteristic AD lesions are generally associated with numerous other lesions, such as neuroinflammation, cholinergic dysfunction, oxidative stress... However, the contribution of each of these lesions is different, and the level of their involvement in the etiology of AD is not clearly established.

Amyloidogenesis:

Histopathological analysis of the brains of AD patients reveals the presence of deposits of a spherical, more or less compact substance; these are amyloid plaques. These amyloid plaques are made up of a polypeptide called amyloid peptide (Aβ). This peptide is a normal catabolic product derived from a protein called APP (amyloid precursor protein).

Amyloid Precursor Protein (APP):

APP is the precursor protein of the amyloid peptide. It belongs to the family of amyloid precursor proteins that includes, in mammals, APP and the proteins APLP1 (APP-like protein 1) and APLP2 (APP-like protein 2) [1]. Only APP generates an amyloidogenic fragment. The gene encoding APP has been located on chromosome 21 (at locus 21q21) and comprises 18 exons [2]. It is expressed in a wide variety of mammalian tissues (brain, kidney, lung, liver, and heart), but is particularly highly expressed in the nervous system, in neurons as well as in certain glial cells [3]. Alternative splicing generates several isoforms of this protein, whose names depend on the number of amino acids. In the central nervous system (CNS), the predominant isoforms are APP695, APP751, and APP770; the APP695 isoform is predominant in neurons [1].

The APP protein has a single transmembrane domain, a very large N-terminal domain (approx. 650-700 amino acids) located in the extracellular space, and a short C-terminal domain (47 amino acids) located in the cytoplasm [4]. The peptide fragment corresponding to the Aβ peptide is a sequence of 42 amino acids. Although the physiological role of APP has not been clearly defined, it is thought to be involved in cell-cell and cell-surface adhesion [5], neurite growth, and synapse formation [6]. Its expression is increased during neuronal differentiation and after neuronal integrity has been compromised. Roles in cell signaling and long-term potentiation have also been suggested [7].

APP metabolism:

After translation and transport to the endoplasmic reticulum, where it undergoes the first stages of glycosylation, APP is transported to the plasma membrane via the Golgi apparatus, where the various post-translational modifications are carried out or completed. At this stage, APP can be secreted or remain anchored to the membrane. From the plasma membrane, a fraction of APP can be internalized and delivered to the endosomes. Once it reaches the endosomal compartment, APP can again be redirected to the plasma membrane or directed to the lysosomes for degradation (Cf.figure1)[8] . In fact, from a cellular point of view, APP can be localized in various membrane structures, such as the endoplasmic reticulum, the Golgi apparatus, certain vesicular organelles, or the cell membrane. It would also appear that APP can undergo different enzymatic cleavages depending on the intracellular compartment in which it is located [9].

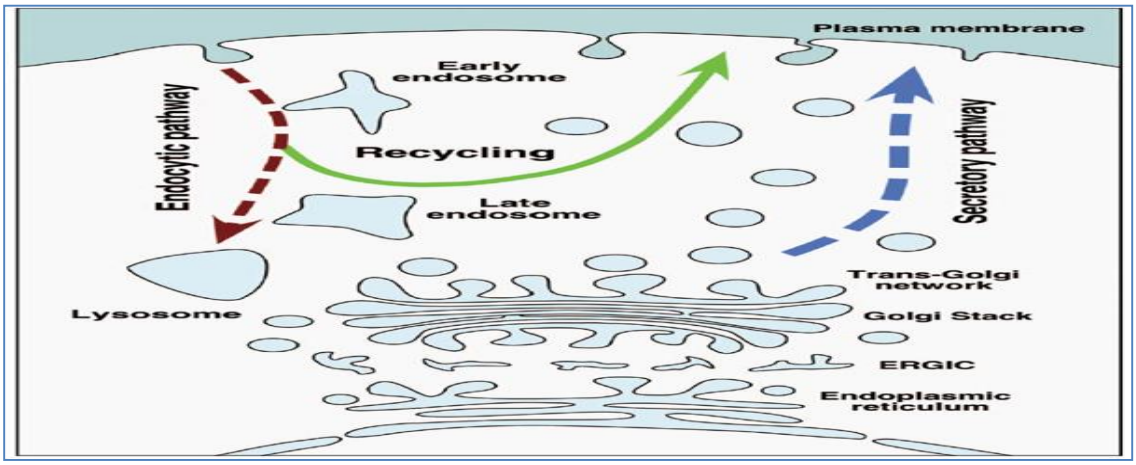

Figure 1: Intracellular APP trafficking. Nascent APP proteins mature via the constitutive secretory pathway. When APP reaches the cell surface, it is rapidly internalized into endosomes. It can then be either recycled to the cell surface or degraded by the lysosomal pathway. APP cleavage by the non-amyloidogenic pathway takes place mainly at the cell surface, where α-secretase is present. The amyloidogenic pathway, on the other hand, transits the organelles of endocytosis, where APP encounters β-secretase **(Kulandaivelu et al., 2006)** [10].

There are two main APP cleavage pathways: a so-called non-amyloidogenic pathway, which does not lead to the formation of amyloid peptides, and an amyloidogenic pathway, which is at the origin of amyloid peptides.

The non-amyloidogenic (or physiological) pathway:

The non-amyloidogenic pathway, which mainly takes place at the cell surface, begins with the action of α-secretase, which cleaves APP within the Aβ fragment itself (Cf.figure 2a), thus preventing the formation of amyloid peptide (Cf.figure 2b). This cleavage takes place in the extracellular space. Three members of the ADAM (A disintegrin and metalloproteinase) family have been considered good candidates for α-secretase activity: ADAM17, also known as TACE (Tumor Necrosis α Converting Enzyme), ADAM10, and ADAM9 [11]. This initial cleavage of APP by α-secretase generates two fragments: the N-terminal sAPPα fragment with neurotrophic properties [12] and the C-terminal C83 membrane fragment (α- CTF). The C83 fragment is a membrane fragment that can be cleaved by γ-secretase, giving rise to two new fragments: P3, with as yet unknown properties, and the AICD (APP intracellular domain) transcription factor [13]. This γ-secretase is a high-molecular-weight multiprotein complex consisting of presenilins PS1 and PS2, nicastrin, and two membrane proteins, Aph-1 (Anterior pharynx-defective phenotype 1) and Pen-2 (Presenilin enhancer 2)[14]. Nicastrin and Aph-1 stabilize presenilins in the complex, while Pen-2 is required for the endo-proteolytic cleavage of presenilins that confers γ-secretase catalytic activity [15].

The amyloidogenic (or pathological) pathway:

The amyloidogenic pathway, which operates mainly within the endosomal/lysosomal system, is characterized by the sequential action of two secretases that cleave APP to release the Aβ peptide (Cf.figure 2c). APP is first cleaved by β-secretase, an enzyme also known as BACE (β-site APP Cleaving Enzyme). BACE can cleave APP at two distinct sites (Cf.figure 2a):

- at aspartate 1, which is the normal cleavage site for amyloid peptides (1-X)
- but also at glutamate residue 11, described as a site of alternative APP cleavage (β'-secretase cleavage), giving rise to shorter amyloid peptides (11-X).

This cleavage leads to the secretion of the N-terminal fragment sAPPβ, which is shorter than sAPPα, and to the formation of the C-terminal fragment C99, consisting of the entire Aβ peptide and the cytoplasmic tail. The C99 fragment then undergoes a second cleavage by γ-secretase, releasing the Aβ peptide into the extracellular medium and the AICD into the intracellular medium.

This cleavage produces variants of the Aβ peptide in Aβ (11-X) and Aβ (1-X) with X=38 to 43 [16]. In healthy subjects, the majority of peptides derived from the amyloid pathway are [17]:

- The short form Aβ-40, the most abundant (90% of secreted peptides), has slow aggregation capacities.
- The long form Aβ-42 (the majority of the remaining 10%), which aggregates more rapidly and is responsible for the main toxic effects.

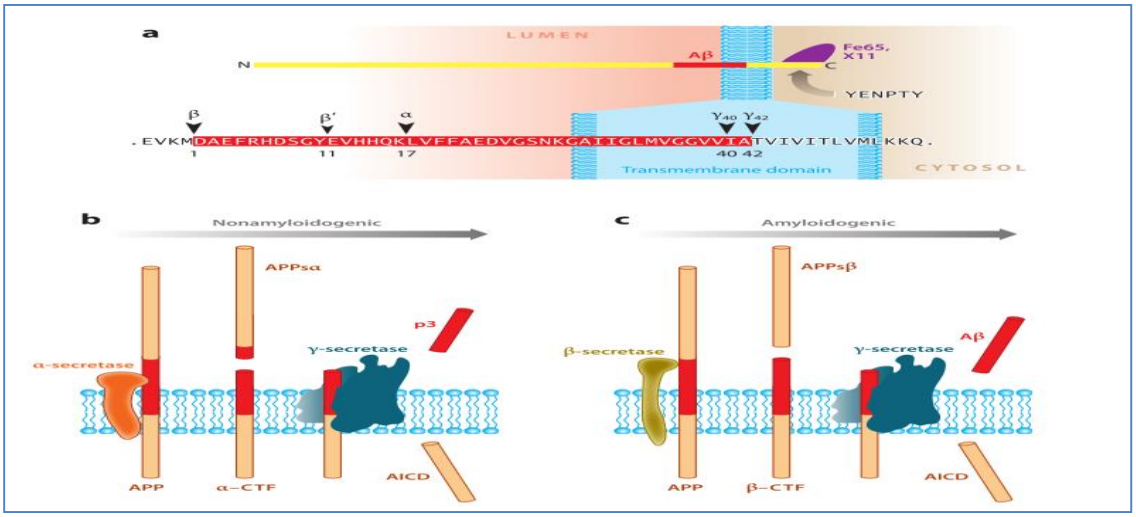

Figure 2: Proteolytic maturation of the APP protein. (a) Schematic representation of the APP structure with the Aβ domain shown in red. Sites of cleavage by α, β, and γ-secretases are indicated using Aβ numbering from the N-terminus (Asp1). (b) The non-amyloidogenic APP cleavage pathway results in sequential processing of APP by membrane α- and γ-secretases. The α-secretase cleaves within the Aβ domain itself, preventing the generation of this peptide. (c) The amyloidogenic pathway of APP maturation is achieved by the sequential action of membrane β- and γ-secretases.

(Adapted from Richard J. O'Brien and Philip C. Wong, 2011)

Under normal conditions, Aβ is degraded by the peptidases IDE (insulin degrading enzyme), neprylisin, and endothelin-converting enzyme [18]. In AD, the overproduction of amyloid peptide is associated with a disturbance in the balance between these two pathways; the amyloidogenic pathway is favoured.

Amyloid peptide and Alzheimer's disease:

Aβ peptides produced by the amyloidogenic pathway differ in the composition of their C- and N-termini, which give them different solubility as well as distinct biological and toxic properties. They are present in the brain in different sizes and aggregation states, ranging from soluble oligomers to fibrillar aggregates.

It should be emphasized that the amyloidogenic pathway does not necessarily lead to pathology. Aβ peptide is produced physiologically in the brain and CSF throughout life. It is the disruption of its production that is pathogenic, with either an overproduction of different forms of Aβ peptides or a specific increase in the level of Aβ peptides. This form is in fact more neurotoxic due to its great capacity to aggregate [19].

The ratio between Aβ40 and Aβ-42 is largely in favor of the short form under physiological conditions (90%). An increase in this ratio is considered to be an early marker of the onset of AD [20]. This change is thought to be responsible for the formation of amyloid deposits in the brain tissue of AD patients. There are two types of amyloid deposits: diffuse plaques and senile plaques [21]. Diffuse plaques are largely composed of Aβ-42 and are not toxic. They are found in various structures of the central nervous system in both patients and healthy individuals. However, they are thought to represent the "pre-amyloid" forms that give rise to senile plaques [21].

Senile plaques, on the other hand, are composed of a mixture of Aβ40-42 peptides aggregated in the form of pleated β-sheets surrounded by a crown of degenerating nerve extensions (dystrophic axons and dendrites) [22]. They are often accompanied by an inflammatory response. They are specific to AD, but no correlation has been shown between the presence of senile plaques and the cognitive impairment associated with AD. These amyloid plaques are present very early in the course of AD, and then after a phase of increase, the number of plaques reaches a plateau and therefore does not follow the pattern of cognitive deterioration observed in AD.

Furthermore, recent data in the literature suggest that the presence of soluble Aβ peptide oligomers may also be of major pathophysiological importance [23]. The presence of these oligomers is more strongly correlated with the cognitive deficits associated with the disease than amyloid plaques[24] .

Regionalization of amyloid plaques:

Initially, amyloid plaques are seen in the neocortex and then spread to the entorhinal cortex, amygdala, insula, cingulate cortex, and hippocampus. At a more advanced stage, certain subcortical nuclei are then affected, such as the striatum, thalamus, and hypothalamus, followed by other brain stem nuclei, and finally the pontus and cerebellum. The evolution of these lesions can be summarized in three phases: an initial neocortical phase, followed by a limbic phase, and finally a subcortical phase (see Figure 3) [25].

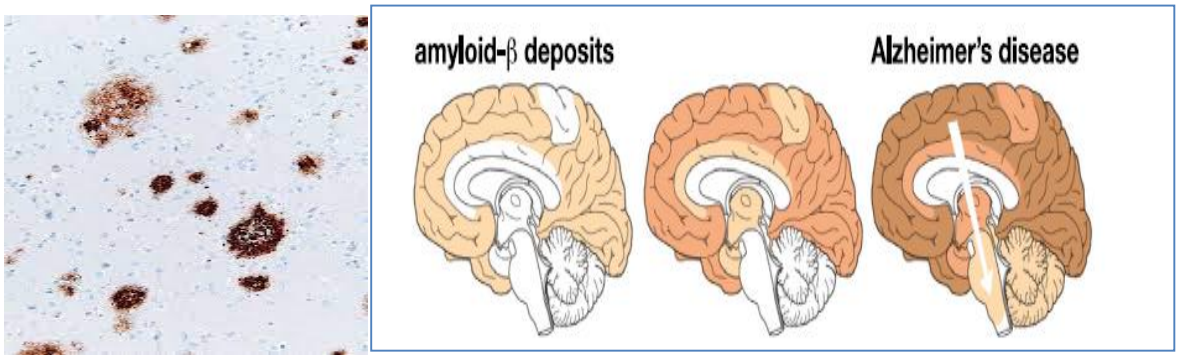

Figure 3: Evolution of amyloid deposits during the development of Alzheimer's disease.
(From Jucker and Walker, 2013)[26]

Neurofibrillary degeneration and Tau proteins:

Neurofibrillary degeneration (NFD) is characterized by the intraneuronal accumulation of fibrillary material known as 'paired helical filaments'. These filaments are mainly composed of hyperphosphorylated Tau proteins [27].

Structure and functions of Tau proteins:

Tau proteins belong to the MAP (Microtubule-Associated Proteins) superfamily of proteins. Mainly expressed in neurons, they are involved in tubulin polymerization, microtubule stabilization, transport of

organelles along microtubules, neurite growth, and also cell signaling by interacting with proteins such as PIP2. The gene coding for Tau proteins is located on chromosome 17, and the primary transcript contains 13 exons. In the human brain, there are six isoforms of the Tau protein resulting from alternative splicing of exons 2, 3, and 10 of the primary transcript.

From a functional point of view, Tau proteins are composed of two domains (see figure 4) [28]:

- a "projection" domain comprising exons 2 or 2+3, which give the protein a different length depending on the isoform. These two highly acidic inserts are followed by a basic region rich in proline. This domain enables the microtubule-bound Tau protein to interact with the plasma membrane and certain organelles, such as mitochondria, thus playing a major role in the structuring of the cytoskeleton.

-a C-terminal microtubule-binding domain comprising repeating motifs. These repeated motifs are sequences of 18 amino acids, denoted R1 to R4, encoded by exons 9 to 12, and enable Tau to bind to the microtubule. This region is thought to be involved in the assembly and stabilisation of microtubules. Isoforms composed of 4 repeated regions (4R) are thought to stabilize microtubules to a greater extent than 3R isoforms.

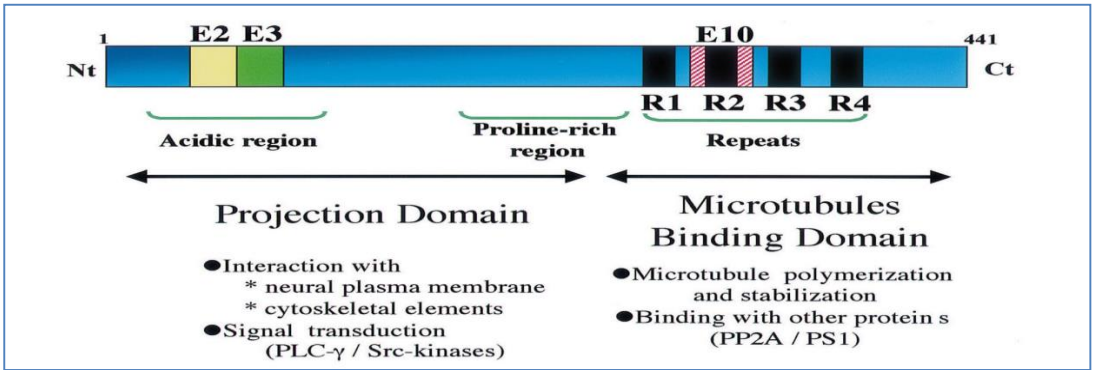

Figure 4: Schematic representation of the functional domains of the longest isoform of the tau protein (441). The projection domain, comprising an acid-rich region and a proline-rich region, interacts with cytoskeletal elements to determine the spacing between microtubules in axons. The C-terminal part corresponds to the microtubule-binding domain and regulates the rate of microtubule polymerization **(Buée et al., 2000)** [28].

Regulation of the phosphorylation state of the Tau protein:

Phosphorylation is the main post-translational modification of Tau proteins. Of the 85 serine and threonine residues present on the Tau protein, 30 are phosphorylated under physiological conditions. These phosphorylations regulate Tau/microtubule interaction and, consequently, microtubule stability [29]. The different phosphorylation states of the Tau protein result from the activity of numerous kinases and phosphatases.

There are many kinases involved in Tau phosphorylation. Among the most common is GSK3β (glycogen synthase kinase 3β), a kinase involved in numerous physiological mechanisms such as cell proliferation and apoptosis.

From a functional point of view, it has been shown that phosphorylation of GSK3β at serines 9 and 389 inhibits the activity of this kinase, whereas phosphorylation at tyrosine 216 increases GSK3β activity [30].

Hyperphosphorylation of the Tau protein and Alzheimer's disease:

Abnormal or excessive phosphorylation is observed in AD. Abnormal phosphorylation results in phosphorylation at sites that, under physiological conditions, are not involved in phosphorylation; this is known as a non-physiological epitope. Excessive phosphorylation corresponds to amplified phosphorylation at one or more physiological sites.

In AD, a number of sites appear to be hyperphosphorylated or abnormally phosphorylated, and this profile concerns all six isoforms of the Tau protein [30]. Immunological methods have shown that these sites are mainly located in the prolin-rich central domain.

Some sites are also found within the repeat region and at the C-terminus. This hyperphosphorylation is thought to reduce the affinity of Tau for microtubules, thereby promoting dissociation of the Tau protein from microtubules. This dissociation leads to disassembly of the microtubules and, therefore, to destabilization of the cytoskeleton, which may be the cause of neuronal dysfunction [31].

In addition, the increase in the number of free hyperphosphorylated Tau proteins will promote the self-assembly of Tau proteins into filaments. Indeed, Alonso et al.(2001)[32] have shown that abnormally hyperphosphorylated Tau proteins isolated from AD patient brains polymerize in vitro to form paired helical

filaments (PHF); the conditions for self-assembly do not require a cofactor. All these results suggest that Tau hyperphosphorylation is probably sufficient for the formation of PHFs and could be the molecular mechanism behind the neurodegenerative lesions in AD. PHFs subsequently aggregate to form Neurofibrillary degeneration (NFDs) [32]. In addition, Tau, like Aβ, is thought to have the capacity to activate the complement system and thus generate an inflammatory response [33].

Regionalization of NFD:

Neurofibrillary degeneration progresses in the cerebral space according to a topography that closely follows the evolution of cognitive deficits. It begins in the medial temporal regions, such as the trans-entorhinal and entorhinal cortices, and the hippocampus, which explain the memory problems for recent events, and extends sequentially to other limbic structures, such as the amygdala and thalamus. It then extends to the cortical associative areas, explaining the overall loss of cognitive functions. Finally, in the most severe cases, it may be detected in the primary sensory, motor, and visual areas, as well as in other subcortical structures such as the striatum and substantia nigra (see Figure 5) [34].

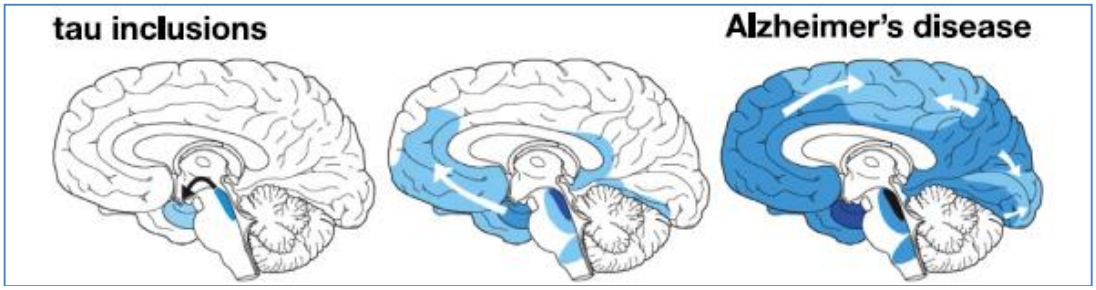

Figure 5: Evolution of DNF deposits during the development of Alzheimer's disease.
(From Jucker and Walker, 2013)[26]

Neuroinflammation:

The involvement of inflammatory mechanisms in the aetiology of AD is now recognized by many authors; it is clearly established that AD is accompanied by an inflammatory response. However, the role of inflammation remains controversial. Although during the early stages of the disease, activation of microglia and astrocytes seems to promote the elimination of Aβ peptides, chronic activation of microglia is accompanied by a concomitant increase in the number of Aβ peptides and Tau phosphorylation.

Today, the sequence in which the lesions described above appear in the aetiology of AD is not known. Only a few hypotheses have been put forward:

- One hypothesis suggests that the overproduction of amyloid peptides is the primary etiological determinant of the disease and that NFD, neuronal loss, neuroinflammation, and dementia are the direct consequences of amyloid deposits. This is the amyloid cascade hypothesis.
- The Tau hypothesis proposes that a deregulation of Tau is at the origin of the neurotoxicity and neurodegenerative processes of AD and that Tau is the key player in the pathogenesis of the disease. This hypothesis is supported by several results, including those of Roberson et al. (2007) [35] obtained in a transgenic AD mouse model overexpressing human amyloid peptide; in this model, even partial reduction of the Tau protein prevents memory problems, despite the persistence of high levels of amyloid peptide.
- Finally, in 2008, Hooper et al. [36] put forward the hypothesis that an increase in GSK3β activity was at the origin of memory impairment, Tau hyperphosphorylation, an increase in Aβ, and the inflammatory response associated with AD.

III. Dysthyroidism and Alzheimer's disease

Some data in the literature suggest that hypothyroidism, the prevalence of which increases with age [37], may be one of the risk factors for AD. It is now clearly accepted that hypothyroidism in adults is associated with learning and memory problems [38], and slight variations in thyroid hormone (TH) levels can lead to cognitive dysfunction and dementia syndrome [39].

In addition, a number of epidemiological studies suggest the existence of a relationship between hypothyroidism and the risk of dementia. This is particularly true of the work by Ganguli and colleagues (1996) [40] on a cohort of 194 people aged 65, who found that hypothyroid patients were three to four times more likely to develop dementia. In 2008, Davis and colleagues [41] revealed tissue hypothyroidism in AD patients; these authors specifically demonstrated a significant decrease in serum T3 levels in the prefrontal cortex of Alzheimer's patients. More recently, Johansson et al. (2013) [42] demonstrated a positive correlation between

TH levels and cognitive performance as assessed by the MMSE and a negative correlation between TH levels and the axonal damage marker Tau. Local hypothyroidism has also been described post-mortem in the hippocampus of AD patients [43].

Literature data obtained in vitro also highlights the role of TH in the processes generating amyloid deposits. These studies show that THs negatively regulate transcription of the Aβ protein [44]. These data are supported by work carried out on rodents, which shows that low levels of TH are accompanied by an increase in the expression of mRNA coding for the APP gene, suggesting that TH modulates Aβ production [45]. Finally, studies have recently shown that hypothyroidism in adult rats promotes the amyloidogenic pathway of APP degradation in the hippocampus [46]. Therefore, THs were suggested to be an effective therapeutic strategy against AD neuropathology through the restoration of memory and cognitive functions [47].

The second potential mechanism contributing to the association of thyroid dysfunction with AD is excessive thyroid hormone levels, which have been associated with toxic effects such as increased oxidative stress on neuronal viability and enhanced neuronal death, which additionally increase the vulnerability of the brain to amyloid toxicity [47]. The third potential mechanism is the direct adverse effect of thyroxine (T4) reduction on cholinergic neurons. Several experimental studies have indicated the significant function of thyroid hormones in the development and preservation of the basal forebrain cholinergic neurons involved in AD [48]. The fourth potential mechanism is the elucidation of the relationship between TRH and the phosphorylation of tau protein. A number of studies have confirmed that a decrease in TRH could improve the phosphorylation of tau and other proteins, which are theoretically involved in the pathogenesis of AD [49]. The fifth potential mechanism is the induction of acetylcholine synthesis and release by TRH, which has been observed in rats, indicating that a decrease in TRH may prompt a reduction in acetylcholine, which plays a significant role in the development of AD [50].

An alternative explanation for a thyroid-AD link is the mediation of risk by vascular factors. Both clinical and sub-clinical, thyroid dysfunction affect cardiovascular risk [51], and in parallel, vascular risk factors have been correlated with an increase in the risk for AD [52]. Thus, through an increase in vascular risk factors such as diabetes, hypertension, heart disease, and smoking, thyroid function may indirectly affect AD risk.

Remarkably, even subclinical HPT may affect the pathogenesis of AD through the modulation of cerebral blood flow [53]. A cohort study on 11 AD patients with subclinical HPT and 141 AD patients without subclinical HPT revealed that cerebral blood flow mainly in the cingulate gyrus and parieto-temporal lobe was reduced in subclinical HPT compared to the controls [53]. Therefore, subclinical HPT may reduce cognitive function through the induction of cerebral hypoperfusion. Park et al. (2019)[54] observed that chronic cerebral hypoperfusion and ischemia promote AD neuropathology by increasing the generation of phosphorylated tau protein and Aβ in the temporal and frontal lobes, respectively. Besides, chronic cerebral hypoperfusion reduces brain glucose metabolism in mice[54]. Therefore, HPT contributes to the pathogenesis of AD by inducing cerebral hypoperfusion.

Effects of AD on Thyroid Function:

It has been shown that AD neuropathology affects thyroid function. The underlying association between AD and hypothyroidism (HPT) is complex, as whether HPT is the cause of AD or HPT as a secondary outcome for AD remains unidentified. In advanced AD, with the involvement of the hypothalamus and anterior pituitary, the hypothalamic-pituitary-thyroid axis is deregulated, leading to HPT [55]. However, Du and Pang (2015)[56] showed that the accumulation of Aβ in early AD contributes to the dysregulation of the hypothalamic-pituitary axis and the development of neuropsychiatric disorders in the prodromal phase.

IV.Conclusion

Taken together, these results suggest that hypothyroidism, and in particular cellular hypothyroidism, thyroiditis, and hyperthyroidism, may be involved in the etiology of AD and thus contribute to the associated cognitive deficits. These data from the literature remain fragmentary but should not be overlooked. When combined with the existing body of knowledge on AD and the role of TH, they open up a new field of investigation.

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