Review

Is Alzheimer's disease a manifestation of brain quantum decoherence resulting from mitochondrial and microtubular deterioration?

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ABSTRACT

The etiology of Alzheimer's dementia is, at best multifactorial. Before the emergence of cognitive impairment, symptoms such as thinning of the cortex, accumulation of β-amyloid, and decreased hippocampal volume are common. Hence, the accumulation of β-amyloid and hyperphosphorylated tau fibrillary tangles are two pathological hallmarks in Alzheimer's disease brains, but antibody therapy aimed to decrease β-amyloid has been a failure and, in most optimistic opinions, may delay somewhat disease progression. However, 31-38 % of subjects develop cerebral micro-hemorrhages in aducanumab therapy, an antibody to the amyloid beta plaque by Biogen. Genetics such as Apo E3/E3 have demonstrated defects in the blood-brain barrier in early-onset dementia. Late Onset Alzheimer's Dementia, has implicated microbe cerebral infections and numerous genetic single nucleotide polymorphisms. However, several cellular biological signatures of Alzheimer's disease have been identified, such as synaptic dysfunction, β-amyloid plaques, hyperphosphorylated tau, cofilin-actin rods, and Hirano bodies which are related to the actin cytoskeleton. Cofilin is one of the most affluent and common actin-binding proteins and plays a role in cell motility, migration, shape, and metabolism. They also play an important role in severing actin filament, nucleating, depolymerizing, and bundling activities. This review summarizes the structure of cofilins appearing after ATP interruptions and deficits in mitochondrial and microtubules and their functional and regulating roles, focusing on the synaptic dysfunction, β-amyloid plaques, hyperphosphorylated tau, cofilin-actin rods, and Hirano bodies of Alzheimer's disease. These findings strengthen our hypothesis that Alzheimer's dementia is characterized by "Quantum Decoherence" resulting from mitochondrial and microtubular deterioration and responding to near-infrared transcranial photobiomodulation to support mitochondrial and microtubule repair, regrowth and neuronal synaptic renormalization.

Keywords: Alzheimer's disease; microtubules, β-amyloid; tauopathy; quantum decoherence; cofilin

1. Introduction

1.1 Synaptic dysfunction

One of the earliest findings in Alzheimer's is synaptic dysfunction which is an immediate cause of the cognitive decline and memory dysfunction (Pelucchi et al., 2022). This occurs before any MRI or PET scan changes on imaging and is defined as dendritic spine pruning on microscopic examination. Dendritic spines are specialized structures in neuronal processes where excitatory synaptic connections occur, and the loss of dendritic spines is directly related to synaptic function loss. Because dendritic spines are easily accessible for both *in vitro* and *in vivo* investigations, they have been extensively examined in Alzheimer's disease (AD) mice models. Dendritic spine dysfunction and loss in AD are thought to be caused by various pathways. Amyloid beta fibrils, diffusible oligomers, and intracellular amyloid beta buildup, for example, have been discovered to change the function and structure of dendritic spines in various ways (Dorostkar et al., 2015).

1.2 Dendritic spine morphology

The morphologic correlates of excitatory post-synapses are dendritic spines. Spines are specialized protrusions from the shaft of a dendrite, where neurons make synapses to receive and integrate information morphologically (Ertürk et al. 2014). Mushroom spines have a large head and a thin neck; stubby spines, which have a huge head but no identifiable neck; and thin spines, which are slender, filopodia-like protrusions without a detectable head, are

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the most common morphologies. At dendritic spines, various specialized synaptic proteins, such as scaffolding proteins and ion channels, are grouped (Nimchinsky et al., 2002; Sheng et al., 2002). Anatomical conditions may influence the size and morphology of the spine. For example, in the reticular nucleus of the thalamus and the gelatinous substance of the spinal cord dorsal horn, longer spines can be seen in brain regions where target axons are positioned farther away from dendrites (Fiala et al., 2002). On the other hand, dynamic changes in spine morphology impact functional features. For example, increasing the spine head size allows for more receptors to be accommodated while shortening and expanding the spine neck reduces the electrical resistance of the spine neck, resulting in bigger excitatory postsynaptic potentials (Yuste, 2013).

1.3 Dendritic spine pathology

Disruptions in the physiologic spine homeostasis cause several neuropsychiatric diseases. The most well-known example is the loss of dendritic spines, which occurs in most neurodegenerative disease. Changes in presynaptic input induced by neuron-autonomous or extra-neuronal causes might cause pathological spine loss (**Fig.1**).

Deafferentation, which results in the loss of whole dendrites (Coleman & Riesen, 1968; Jones Thomas,1962; Matthews & Powell, 1962), or sensory deprivation, which results in more complicated changes: a retinal lesion, for example, results in the total replacement of spines in the deafferented cortex (Keck et al. 2008). Spine loss can be caused by neuron-autonomous reasons such as pathological NMDA receptor activation during excitotoxicity (Halpain et al., 1998; Hasbani, 2001) or disruption of dendritic trafficking. Disruption of local protein production at the spine, for example, can change spine density and morphology (Tolino et al., 2012). Trauma or inflammation are two examples of extra-neuronal causes of spine loss, which act through various processes. Trauma produces calcineurin-mediated spine loss, followed by spine overgrowth (Campbell et al., 2012). Inflammation stimulates the release of interleukin 1, which counteracts the effects of BDNF, resulting in spine degeneration (Tong et al., 2012). Tumor necrosis factor (TNF) from activated microglia promotes phosphorylation and upregulation of AMPA receptors, which causes excitotoxicity (Ferguson et al., 2008; Leonoudakis et al., 2008), resulting in spine loss (Centonze et al., 2009). Finally, changes in the extracellular matrix composition are linked to synapse loss (Morawski et al., 2012).

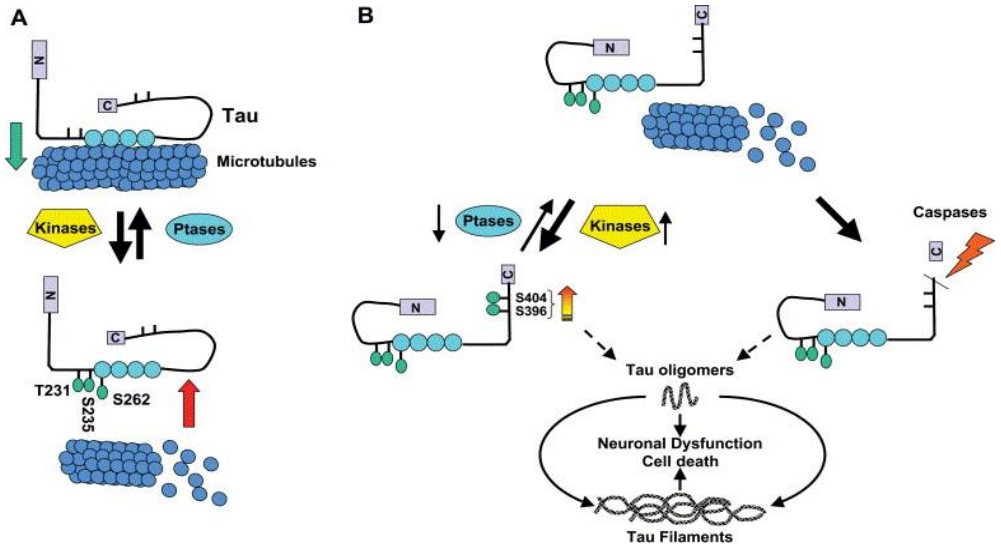

Figure 1 *Illustration of the role of tau phosphorylation in regulating tau function in a physiological setting (**A**) or a pathological situation (**B**). (**A**) Under physiological conditions, there are balanced and dynamic changes in tau phosphorylation, which modulate tau's interactions with microtubules allowing for appropriate neuronal function. Several different protein kinases and phosphatases likely work in concert to appropriately regulate tau phosphorylation. In particular, phosphorylation at Ser^{262} and Thr^{231}/Ser^{235} likely play key roles in regulating tau microtubule interactions. Normal kinase and phosphatase activities keep tau–microtubule interactions tightly regulated. (**B**) In a pathological state, certain toxic insults lead to a dysregulation in the balance in the activities of specific kinases and phosphatases, which results in tau being more phosphorylated at the critical microtubule regulatory sites leading to increased levels of "free tau" that is not bound to microtubules. The decrease in tau's binding to microtubules and other physiologically relevant proteins, coupled with an increase in self-association, contributes to the impairment of neuronal function and, eventually, cell death. This model was modified from one originally proposed by Abraha et al. (2000).*

2. Molecular-level changes in AD

21. Evidence of synapse loss in AD

In the 1990s, a ground-breaking study used electron microscopy to examine samples from people with clinically apparent AD and associated synapse numbers with scores from the Mini-Mental Status examination, a cognitive function test. Compared to cognitively normal controls, patients with AD had a considerable loss of synapses, and their cognitive abilities were correlated with synapse density (DeKosky et al., 1990; Terry et al., 1991).

Based on post-mortem tissue analysis, researchers could examine brain regions not amenable to biopsy. Individuals with early stages of AD, for example, had significantly fewer synapses in the inferior temporal gyrus, which is important for verbal fluency (Scheff et al., 2011), the CA1 region (Scheff et al., 2007), the dentate gyrus (Scheff et al., 2006), and the posterior cingulate gyrus, which is a cortical region affected early in the onset of AD (Scheff et al., 2015). Synaptophysin, a presynaptic marker, was lost in immunohistochemistry (Masliah et al., 1989). Furthermore, a recent postmortem investigation in the brains of 5 AD patients employing intracellular Lucifer yellow injections indicated that intraneuronal tau clumps are linked to a gradual modification of dendritic spines (Merino-Serrais et al., 2013).

In vivo PET imaging studies provide more evidence for the loss of synaptic function. The abundance of certain neurotransmitter receptors in various brain areas is measured using radionuclide-labeled agonists for these receptors. The loss of 42 nicotinic acetylcholine receptors in the medial frontal cortex and nucleus basalis magnocellularis was discovered in one study, indicating the loss of cholinergic synapses. Increased amyloid levels and a loss of key cognitive abilities were linked to the loss of 42 receptors (Okada et al., 2013). CB1 cannabinoid receptors, on the other hand, were unaffected (Ahmad et al., 2014), while 5HT4 serotonin receptors increased as amyloid deposition increased (Kendziorra et al., 2011; Madsen et al., 2011). In the late stages of AD, 5HT1 serotonin receptors were depleted (Mizukami et al., 2011). These synaptic alterations have far-reaching consequences on a larger scale, resulting in paradoxical hyperexcitability and disruption of large-scale networks (Grady et al., 2001; Sperling et al., 2010; Sperling et al., 2009), which are assumed to be functional correlates of clinically noticeable symptoms such as decreased memory and cognition.

The pathogenesis of dendritic spine loss is unknown. The initial causal component leading to increasing synaptic damage is likely to be amyloid beta accumulation (Hardy et al., 2002). However secondary neuropathological changes, such as tau hyperphosphorylation or inflammation and subsequent dendritic and axonal dysfunction, can cause synaptic damage on their own or worsen amyloid beta-induced damage.

2.2 B-amyloid, an overvalued AD biomarker

β-amyloid is one of many enzymatic cleavage products of APP (Nhan et al., 2015), and its secretion into the extracellular environment is boosted by neuronal activity (Cirrito et al., 2005; Kamenetz et al., 2003) via extrasynaptic NMDA receptor activation (Bordji et al., 2010). To be more precise, β-amyloid refers to several different chemical substances, depending on the cleavage sites and post-translational changes such as oxidation, phosphorylation, nitration, racemization, isomerization, pyroglutamylation, and glycosylation (Kummer & Heneka, 2014). For example, the 42 amino acid form (A1–42) aggregates more readily than the 40 amino acid version (A1–40). Changes at the N-terminus further alter the biophysical characteristics of the protein. Pyroglutamate β-amyloid (Ap3–42), which has a cyclized glutamate residue at the N-terminus, has a higher proclivity for aggregate formation (Schilling et al., 2006) and appears to be specialized for fibrillar plaques (DeMattos et al., 2012). β-amyloid can be found in oligomeric and fibrillar forms in extracellular and intracellular compartments. These kinds have been linked to synaptic injury, which will be examined further in the following subsections.

2.3 Beta amyloid plaques

The extracellular deposits of β amyloid are known as amyloid plaques. Plaques might present histologically as diffuse plaques that lack fibrils and are only identifiable in immunohistochemical stains utilizing antibodies directed against APP epitopes. Alternatively, they can appear as cored plaques with a fibrillar core and

a diffuse, non-fibrillar halo surrounding them. In H & E sections, the fibrillar core can be seen, and dyes specialized for fibrillar aggregates, such as Congo red or thioflavin S, can be used to stain it. PET tracers such as Pittsburgh compound B or florbetaben are used in clinical settings to detect fibrillar amyloid beta.

In contrast, fluorescent derivatives, such as methoxy-X04, are employed in animal investigations for *in vivo* microscopy. Most clinical and experimental *in vivo* studies have focused on fibrillar amyloid deposits since these agents only detect fibrillar protein aggregates. There is plenty of evidence that fibrillar amyloid-beta damages synapses. Fibrillar amyloid plaques are often surrounded by dystrophic neurites in human instances, giving rise to the so-called neuritic plaque appearance in silver stains or immunohistochemical stains utilizing AT8 antibodies against hyperphosphorylated tau protein. The location and extent of dense neuritic AT8-staining in the form of neuropil threads occur distant from plaques in human disease, and the location and extent of this staining are decisive measures to obtain the neuropathological staging according to the Braak and Braak criteria (Braak and Braak, 1991), which correlate best with cognitive status. Some, but not all, mouse models of amyloidosis show comparable neuritic plaques that can be detected by AT8 antibody staining or silver impregnation, just as they can in humans (Cheng et al., 2004; Chishti et al., 2001; Radde et al., 2006; Richardson et al. 2003, Sturchler-Pierrat et al., 1997). Neuritic pathology in mouse models of amyloidosis, in contrast to human disease, is invariably localized to the immediate area of fibrillar plaques, while neuropil threads distant from plaques have not been detected. This could explain why changes in spine density of layer 3 and 5 pyramidal neurons are only visible near plaques in various animal models of AD that overexpress mutant human APP and/or presenilin (Wu et al., 2010; Koffie et al., 2009; Kirkwood et al., 2013). In one APP/PS1 mouse model, researchers discovered that spine degeneration occurred at least 4 weeks after plaque formation (Bittner et al., 2012). Even though the transgenes are the same, the processes that cause spine loss may differ in mouse models (Zou et al., 2015).

Nonetheless, spine loss was seen in several mouse models that appeared to be independent of plaques (Bittner et al., 2010; Lanz et al., 2003). This spine loss occurred only in dystrophic dendrites in the triple transgenic mouse model co-expressing mutant APP, PS1, and tau that was analyzed, with an intracellular buildup of both soluble amyloid beta and hyperphosphorylated tau protein (Bittner et al., 2010). Because amyloid plaques cause significant axonal damage, subsequent spine loss due to presynaptic failure (Adalbert et al., 2009) is quite likely in the areas where damaged axons project. Moreover, chronically changed synaptic input in aged APP/PS1 mouse may influence overall dendritic complexity and length while dendritic spine density remains unaffected (Šišková et al., 2014). In the absence of a considerable loss in the spine density of layer 3 and 5 neurons, these scenarios might explain a minor decrease in overall synapse density in some animal models of amyloidosis. In addition, functional changes in neurons proximal plaques hint at a direct or indirect role for fibrillar amyloid beta in synaptic function impairment (Busche et al., 2008). Disturbance of intracellular calcium dynamics (Chakroborty et al., 2011; Kuchibhotlaet al., 2008) or mitochondrial integrity (Xie et al., 2013) could represent functional linkages between neuronal and synaptic dysfunction. Furthermore, near plaques, perisomatic GABAergic terminals are destroyed[1], possibly contributing to hyperexcitability and spine loss.

In a nutshell, hallmark AD neuropathology includes extracellular amyloid plaques composed of the amyloid-β protein (Aβ), intracellular neurofibrillary tangles (NFTs) composed of the hyper-phosphorylated microtubule-associated protein tau (MAP-tau), and microtubule destabilization. While early-onset autosomal dominant AD genes are associated with excessive Aβ accumulation, cognitive impairment best correlates with NFTs and disrupted microtubules. In a molecular modeling paper (Craddock et al., 2012), a molecular mechanism was proposed, and a mathematical model was presented, which links Aβ and NFT pathologies whereby the sequestration of zinc by

[1] https://www.alzforum.org/news/conference-coverage/pursuit-toxic-tau

Aβ oligomers and plaques drives Aβ aggregation and, importantly, disrupts zinc homeostasis in zinc-enriched

brain regions vulnerable to AD pathology. This leads to intra-neuronal zinc levels, which are either too low or excessively high, outside the normal levels. The mathematical model involved time-dependent equations showing zinc distribution in extra-neuronal Aβ deposits can reduce intra-neuronal zinc binding to microtubules, destabilizing microtubules. The connection described by this model is based on β-amyloid-induced alterations in zinc ion concentration inside neurons, which result in altered stability of polymerized microtubules, whose downstream effect is the loss of affinity between MTs and MAP-tau. The proposed theory supports novel AD therapeutic strategies targeting intra-neuronal zinc homeostasis and MT dynamics to prevent neurodegeneration and cognitive decline. This also provides a connection between b-amyloid aggregation and tauopathy.

3. Hyperphosphorylated tau protein

Tau is a family of proteins linked to microtubules discovered in the brain of Alzheimer's patients with neurofibrillary tangles (NFT) (AD). Weingarten et al. (1975) discovered a heat-stable protein that promotes microtubule formation. Subsequently, Cleveland et al. (1977) discovered that tau is a phosphoprotein that, by phosphorylation, inhibits its capacity to drive microtubule construction. Cleveland et al. (1977) observed that tau was hyperphosphorylated in brain samples from AD patients. This could cause a malfunction in microtubule assembly and self-assembly into paired helical filaments (Iqbal et al., 1986).

MAP-tau enhances the stability of axonal MT bundles and participates in the regulation of axonal growth and transport. MAP-tau is phosphorylated during both physiological and pathological processes, but it is unknown whether the mechanisms involved in normal and abnormal hyperphosphorylation of MAP-tau are related. Most potential phosphorylation sites comprising 80 serine, threonine or tyrosine residues on MAP-tau are located in the proline-rich domain and the C-terminal region. Approximately 45 phosphorylated sites have been identified in the AD brains, which represent over 50% of all residues that can be phosphorylated have been phosphorylated (Braak & Braak, 1997). Phosphorylation is performed by *kinases*, while dephosphorylation is by *phosphatases*. The protein kinases (PK) can be grouped into three major classes: (1) PDPK(Proline Directed Protein Kinases), (2) Non-PDPK (Non-Proline Directed Protein Kinases) and (3) TPK (Tyrosine Protein Kinases). Phosphorylation events on MAP-tau are expected to be sequential and may be triggered by an imbalance in the activity of specific protein kinases or phosphatases. The neuropathological cascade for neurofibrillary tangle formation in AD starts with the tau protein becoming highly hyperphosphorylated (Goedert et al., 1995; Avila et al., 2000), which leads to aggregation of MAP-tau, along with MAP2 and other MAPs into insoluble protein masses. MAP-tau aggregates further coil into paired helical filaments and adopts a β-conformation, causing the entire protein mass to transform into neurofibrillary tangle material (Mandelkow et al., 2007). Hyperphosphorylated MAP-tau significantly alters microtubule dynamics blocking the assembly of new microtubules (Li et al., 2007). This suggests that MAP-tau hyperphosphorylation is responsible for MT dysfunction in AD. Interestingly, even healthy neurons from AD brains (i.e., those lacking neurofibrillary tangles or tau filaments) exhibited microtubule defects (Cash et al., 2003). While the reason for the emergence of primary defects in MTs remains elusive, it is plausible that MTs have become a common target for degradation in cellular aging processes (Raes, 1991).

Frontotemporal dementia with Parkinson's is a group of rare autosomal degenerative illnesses characterized by inappropriately phosphorylated tau induced by a tau gene mutation on chromosome 17q21. Other tauopathies include progressive supranuclear paralysis, chronic traumatic encephalopathy, and Lytico-Bodig disease (Guam's Parkinson-dementia complex, tangle-predominant dementia, with Alzheimer's-like NFTs but no plaques). Tauopathies include ganglioglioma and gangliocytoma, meningioangiomatosis, sclerosing subacute panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, and lipofuscinosis (Poorkaj et al., 1998; Thibodeau et al., 2009). Because of their pathophysiology, Kertesz (2007) suggests that many complex illnesses are a spectrum of presentations of the same disorder). Tau that has been inappropriately hyperphosphorylated causes neurofibrillary alterations. In all of these tauopathies, this anomaly is thought to be the cause of

dementia, dubbed the tau neurotoxic condition. The authors believe inhibiting aberrant tau hyperphosphorylation is a promising therapeutic target (Takeuchi, 2011).

Tau protein seems to be a prerequisite for neuronal damage, as tau knockout mice are immune to neuronal insults mediated by NMDA receptor-dependent excitotoxicity and those caused by β-amyloid. The degree of tau pathology is more closely linked to cognitive decline than amyloid pathology. Furthermore, tauopathies are a set of neurodegenerative illnesses characterized by tau protein mutations that result in hyperphosphorylated tau protein accumulation without an associated underlying pathology. Overexpression of wild-type human tau in experimental mice is sufficient for producing neurofibrillary tangles and age-dependent reductions in spine head sizes (Adalbert 2009). Similarly, when introduced, P301S9 mutant human tau promotes inflammation and spine loss (Takeuchi, 2011). These findings imply that hyperphosphorylated tau may cause synaptic injury on its own. Furthermore, a recent study on 5 AD patients found that pyramidal neurons in the parahippocampal cortex and CA1 neurons with intraneuronal neurofibrillary tangles had fewer spines in distal portions of the dendritic tree (Merino-Serrais et al., 2013). Loss of spinophilin-positive puncta in the CA1 field and area 9, which are indicators of dendritic spines, was linked to cognitive decline and tau pathology in another investigation[1].

Tau protein is primarily found in axons connected with the cytoskeleton in a physiological sense. Tau's subcellular location is determined by its physiological phosphorylation pattern: For example, tau is localized to the nucleus by one phosphorylation sequence, while another is necessary during mitosis (Nizzari et al., 2012). Tau translocation to postsynapses is increased by LTP induction or pharmacological activation of synaptic activity (Burnouf et al., 2013). This localization pattern is disrupted by hyperphosphorylation of tau (Nizzari et al., 2022; Zempel et al., 2013). Interestingly, there is some evidence that APP is involved in tau phosphorylation (Nizzari et al., 2012). Splicing (Liu et al., 2013) and post-translational enzymatic cleavage (Rosenmann et al., 2014) impact tau's subcellular location.

Tau truncation by specific proteases, for instance, may increase tau toxicity and enable hyperphosphorylation (Zhang et al., 2014). Distinct truncation and hyperphosphorylation patterns result in diverse tau conformations, or "strains," which are responsible for different tauopathies (Sanders et al., 2014). Furthermore, these tau strains may be spread in a prion-like way from human tissue to vulnerable mouse models while retaining their identity (Clavagnera et al., 2013; Sanders et al., 2014). A distinct pathogenic tau proliferation has been found within experimental animals' brains. There, tau pathology spreads synaptically from neuron to neuron (De Calignon et al., 2012; Dujardin et al., 2014; Liu et al., 2012), which could be the mechanism behind the AD-specific spreading pattern of tau pathology (Braak et al., 2006).

4. Cofilin-actin rods and Hirano bodies

However, several cellular biological signatures of AD have been identified, such as synaptic dysfunction, β-amyloid plaques, hyperphosphorylated tau, cofilin-actin rods, and Hirano bodies which are related to the actin cytoskeleton. Cofilin is one of the most affluent and common actin-binding proteins and plays a role in cell motility, migration, shape, and metabolism. It also plays an important role in severing actin filament, nucleating, depolymerizing, and bundling activities. Loss of dendritic spines leads to the impairment of synaptic transmission as the dendritic spines are the primary sites for receiving information and cellular substrates for synaptic plasticity (Cummings et al., 2015), the main cytoskeletal protein found in the dendritic spines (Matus et al., 1982; Cohen et al., 1985) and its depolymerization is dynamically modulated by cofilin-1. Cofilins are an important Actin Binding Protein (ABP) and consist of five members, including cofilin-1, cofilin-2, destrin, depactinm, and actophorin, that have been characterized in various organisms ranging from eukaryon to mammal. Due to the important role of synaptic function in brain function (Malenka et al., 1994; Zucker et al., 2002; Südhof, 2004), any dysregulation or loss of synaptic function may lead to neurodegenerative diseases such as AD. Decreased glucose utilization has been observed in humans through PET imaging before the emergence of overt symptoms, suggesting that synaptic dysfunction precedes AD pathogenesis (Jack et al., 2013; Jack et al., 2013b). Synaptic function is

multifaceted and relies on factors such as spine morphology, synaptic plasticity, neurotransmitter release, learning, and so on (Richmond, 2005).

Because dendritic spines are the key sites for receiving information and cellular substrates for synaptic plasticity, their loss causes the synaptic transmission to be impaired (Cummings et al. 2015). F-actin is the main cytoskeletal protein found in dendritic spines (Matus et al., 1982; Cohen et al., 1985), and its depolymerization is dynamically modulated by cofilin-1 (Okamoto et al., 2007; Hotulainen et al., 2009; Bamburg et al., 2010; Bernstein & Bamburg 2010; Gu et al., 2010), the WAVE complex, and other factors cause actin polymerization (Welch et al., 1997; Bel et al., 2008). ADF/cofilin-induced actin filament disintegration keeps spine length and shape in check (Bosch et al., 2014). Active cofilin is supplied to the spine in the early phase of remodeling spine substructures, and cofilin then forms a stable complex with F-actin to stay at the spine and consolidate spinal expansion during the stability phase (Bosch et al., 2014). Meanwhile, in the dentate gyrus, cofilin-1 is inactivated by an increase in Ser3 phosphorylation, which is accompanied by a change in dendritic spine shape (Nader et al., 2019). Active cofilin binds to actin and accelerates the conversion of F-actin to G-actin, which is triggered by dephosphorylation (Bamburg and Bernstein, 2016). Suppression of cofilin phosphorylation inactivates the Rac1/cofilin pathway, resulting in the hippocampus losing its dendritic spine (Yang et al., 2018). Similar to the shift in phosphorylation and redistribution of cofilin-1 in an AD rat model, the density of dendritic spines and dendritic complexity rises (Han et al., 2017). Cofilin-1 deficiency results in fewer thin spines and shorter dendritic protrusions (Hotulainen et al., 2009). In addition, as seen in cofilin-1 mutant mice, both the breadth and length of the spinal head are increased in primary hippocampus cultures. In hippocampus slices from cofilin-1 mutant mice, there was also an increase in spinal density and hypertrophy (Rust et al., 2010). When the normally dormant cofilin-1 is overexpressed in hippocampus cultures, mature spines and densities are boosted (Shankar et al., 2007; Gu et al., 2006).

4.1 Cofilin in Alzheimer's dementia

Aβ plays a crucial role in cofilin deregulation through the LIMK1 pathways. **Fig. 2** provides a graphical illustration of the AD processes in which cofilin is centrally involved. We discuss these mechanisms below.

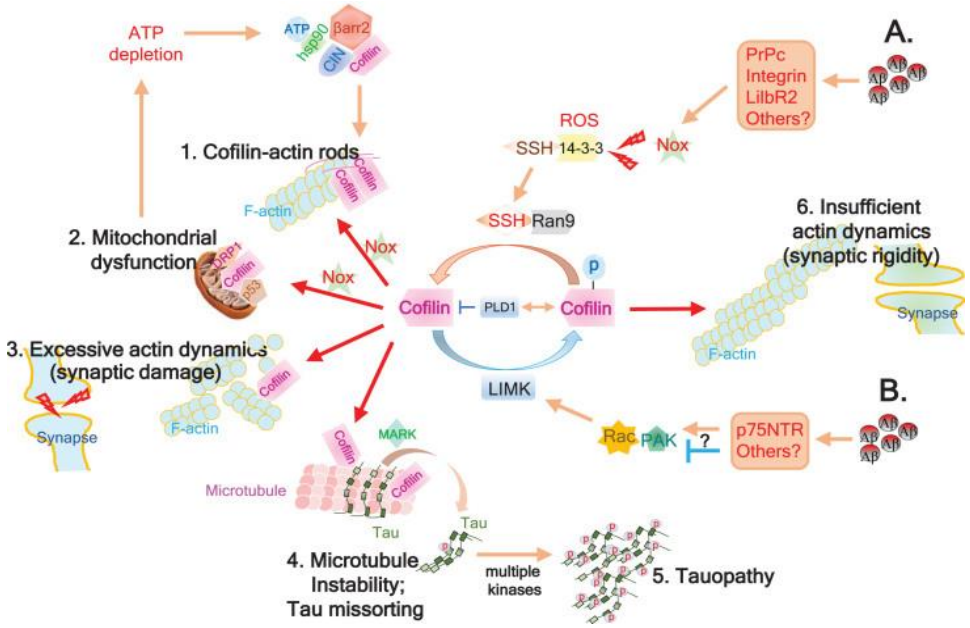

Figure 2 *Schematic illustration of the model of Aβ-induced cofilin deregulation in AD.*

Heredia et al. (2006) demonstrated that $A\beta_{1-40}$ and $A\beta_{25-35}$ fibrils induce the activation of LIMK, which leads to cofilin inactivation. Another study demonstrated, through the injection of $A\beta_{1-40}$ fibrils into rat brains, that cofilin increased activation rather than inactivation (Bie et al., 2018). Mendoza-Naranjo et al. (2012) showed that LIMK1 was activated by $A\beta_{1-42}$, which is paradoxically related to the increased cofilin activation.

4.2 Mitochondrial cofilin translocation

Through direct transfer to mitochondria, activated cofilin also plays a role in mitochondrial dysfunction. Cofilin becomes oxidized on multiple cysteine sites in response to oxidative stress, facilitating intramolecular disulfide bridging (Klamt et al., 2009). This causes cofilin to lose its affinity for actin and translocate to mitochondria, where it promotes the opening of the permeability transition pore, causing swelling, a reduction in mitochondrial membrane potential, and cytochrome c release. Surprisingly, this occurs without the involvement of Bax. Cofilin dephosphorylation (or activation) is essential for its translocation to the mitochondria and oxidant-induced apoptosis, in addition to oxidation. When cysteine mutagenesis prevents cofilin oxidation, oxidant-induced apoptosis is also prevented. Furthermore, siRNA-mediated suppression of endogenous cofilin reduces both oxidant and staurosporine-induced apoptosis, demonstrating that cofilin is required for mitochondrial apoptosis (Klamt et al., 2009; Wang et al., 2008; Chua et al., 2003).

5. Quantum aspects of neuronal synchronization

Hameroff and Penrose (1996, 2014) have been the main proponents of mechanisms involving quantum computations in brain microtubules (see also Hameroff, 1998). These theories have encountered criticism, especially regarding the thermal decoherence of quantum states at physiological temperature, which would make it impossible to perform physiologically meaningful quantum computation in the brain (Tegmark, 2000). However, the issue is still far from settled. Quantum mechanical models of neurocognitive states nonetheless remain attractive for many reasons, not least of which is that quantum mechanics deals with the parallel calculations of probability amplitudes similar to the way that cognitive states simultaneously take into account probabilities affiliated with a multitude of past associations and future anticipations. Eccles (1986) hypothesized that quantum mechanical wavefunctions may cause "mental events" to be transformed into neural events, such as neurotransmitter release by synaptic connections (see also Beck & Eccles, 2003).

Similarly, Scott (1999) argued that a neuron might rely on quantum effects to attain non-deterministic computational properties. Quantum mechanical and molecular dynamics modeling have been applied to the study of receptor proteins and ion channels, indicating that quantum mechanical properties fundamentally govern how ligands bind to receptors and ion channels operate (Summhammer et al., 2012; 2020). Macroscopic quantum coherence has been proposed to occur in other cytoskeletal complexes. Matsuno & Paton (2000) have argued for entangled quantum coherence attaining macroscopic proportions during the slow hydrolysis of ATP, which drives the sliding of actin-myosin complexes with muscle contraction. Explaining the complex basis of macroscopic coherence in the brain remains one of the ultimate frontiers in neuroscience, and satisfactorily accomplishing this task will greatly facilitate understanding of higher neurocognition. As Hameroff (1987) suggested, tubulin itself might act as a qubit underlying biomolecular consciousness. Consistent with the notion that biomolecular computations by tubulin underlie consciousness are the findings that the inhaled anesthetic, halothane, binds to both α- and β-isotypes of tubulin (Craddock et al., 2012b). To the extent that coherence represents a potential correlate of contents of consciousness, collapse (or decoherence) would correspond with the transitions or pauses between those conscious moments.

6. Photobiomodulation

Photobiomodulation was discovered by Mester et al. (1976) using a ruby laser to destroy cancerous tumors in rats. However, with significantly lower-power laser experiments, hair growth (Andres et al., 20)15) and wound healing (Hamblin, 2016) near tumor sites in mice was observed instead. Subsequently, these methods were applied to human patients with skin ulcers (Anders et al., 2019; Khoo et al., 2021). This treatment has been referred to as low-level laser therapy (LLLT) or low-level light therapy. These treatments include the usage of LEDs instead of lasers. An alternative term for this

modality is photobiomodulation (PBM) or PBM therapy (PBMT), which is not limited to LLLT (Ding et al., 2021). In connection with the topic of this review, a multitude of studies involving the application of PBMT to the treatment of patients with neurodegenerative diseases has been reported in recent years (Hamblin, 2016b), demonstrating very encouraging results in both clinical and animal (Purushothuman et al., 2014) trials. This application is typically referred to as brain PBM (Salehpour et al., 2018; Hennessy & Hamblin, 2016) and commonly uses transcranial PBM (tPBM). For example, Cardoso et al. (2022) reported an improved inflammatory response in the brain of aged rats, while Xuan et al. (2014) found that mice experienced enhanced memory and learning after traumatic brain injury following an application of tPBM. Transcranial PBM has also been used to treat major depressive disorder (Caldieraro & Cassano, 2019).

Importantly, PBMT to treat AD and dementia patients was found to improve the sleep and mood characteristics of these patients (Figueiro et al., 2014). A model providing a mechanistic explanation of the interactions of light with sleep and circadian rhythm patterns resulting in positive effects on mood and cognition has been published (LeGates et al., 2014). A separate review of PBM as a therapeutic modality in treating AD has also been published (Cardoso et al., 2020). Moreover, significant improvements due to the clinical application of tPBM in treating Parkinson's disease patients have been recently reported (Liebert et al., 2021). The effects of near-infrared (NIR) PBM on human brain activity using MRI have also been published (El Khoury et al., 2019).

Moreover, supplementation of tPBM with intranasal PBM has been shown to yield marked improvements in the cognitive abilities of dementia patients (Saltmarche et al., 2017). A mechanistic connection between these brain PBM studies has been very recently shown (Staelens et al., 2022) by an investigation into the effect of PBM on tubulin and microtubule dynamics which, as argued abundantly above, are integral structures of neurons responsible for many functions and potentially involved in quantum mechanical interactions. Therefore, their sensitivity to photons in the visible and NIR range may be indicative of quantum effects at work. In this study, living cells, tubulin, and microtubules in buffer solutions were exposed to near-infrared (NIR) light with a wavelength of 810 nm pulsed at a frequency of 10 Hz. In the first group of experiments, AC ionic conductivity in the 50–100 kHz range of HeLa and U251 cancer cell lines exposed to PBM for 60 minutes showed increased resistance compared to the control experiments. In the second group of experiments, the polymerization of microtubules under exposure to PBM was monitored. Exposure of TaxolTM-stabilized microtubules to the LED at 810 nm, with a power density of 25 mW/cm^2 pulsing at 10 Hz for 120 minutes, resulted in the gradual disassembly of microtubules. In the third group of experiments, turbidity measurements throughout the tubulin polymerization process were used to quantify the rate and amount of polymerization. Compared to the unexposed control samples, a slower rate and reduced overall amount of polymerization in the low-concentration tubulin samples exposed to PBM for 30 minutes were found with the same parameters as mentioned above. Paradoxically, the opposite effect was observed in the 45.5 μM tubulin samples, demonstrating a remarkable increase in the polymerization rates after exposure to PBM. These results on the effects of PBM on living cells, tubulin, and microtubules validate the modulating effects of PBM.

7. Conclusions

We have discussed the stages and pathological markers of Alzheimer's dementia, which is now thought to begin with increased blood-brain barrier dysfunction followed by the following: Synaptic dysfunction, β-amyloid plaques, hyperphosphorylated tau, cofilin-actin rods, and Hirano bodies which are related to the actin cytoskeleton. Cofilin is one of the most affluent and common actin-binding proteins and plays a role in cell motility, migration, shape, and metabolism. It also plays an important role in severing actin filament, nucleating, depolymerizing, and bundling activities. In this review, we have summarized the structure of cofilins appearing after ATP interruptions and deficits in mitochondrial and microtubules and their functional and regulating roles, focusing on the synaptic dysfunction, β-amyloid plaques, hyperphosphorylated tau, cofilin-actin rods, and Hirano bodies of AD. Recently we have

recognized that these findings strengthen our hypothesis that Alzheimer's dementia is characterized by "*Brain Quantum Decoherence*" from mitochondrial and microtubular deterioration which requires transcranial photobiomodulation with coherent light (photons) to repair and reenergize mitochondria and microtubules.

Many biological processes (including the conversion of energy into forms that can be used for chemical changes) are quantum mechanical, as we highlighted in previous work on quantum biophysics. In chemical processes like photosynthesis, olfaction, and cellular respiration, such processes include chemical reactions, light absorption, the formation of excited electronic states, the transmission of excitation energy, and the transfer of electrons and protons (hydrogen ions). In our discussion, we used the Orch OR model of quantum consciousness (Hameroff & Penrose, 2014) as viable and argued that, despite various criticisms, quantum computations in brain microtubules, as claimed by the Orch OR model, provides a framework for better understanding of the molecular basis of AD as caused by quantum decoherence at a sub-neuronal level. Observing gigahertz-range electromagnetic excitations in proteins (Genberg et al., 1991) provides experimental support for Fröhlich-like coherent excitations in biological systems. Once thought to be necessary only for cell mobility, cell division (mitosis), and the establishment and maintenance of cell structure and function, microtubules now appear to play additional important roles in living cells, especially neurons. Indeed, they have been experimentally demonstrated to possess highly complex ionic and possibly electronic conduction properties (Kalra et al., 2020; 2020b; Santelices et al., 2017).

Moreover, membrane structure interacts with mechanical signaling and communication activities via ion transfer processes and 'second-messenger' chemical signals. With the involvement of microtubules and actin filaments, membranes can transport electrical impulses via ionic cable-like transmission processes owing to their ability to perform information storage and information processing (Craddock et al., 2012c). The impact of electrical, electronic and photonic signals on microtubules is better understood now because of the above experimental advances and recent tryptophan fluorescence studies (Kalra, 2022), which offer more credence to the role of microtubules as a "subcellular substrate for quantum consciousness."

Mitochondrial damage in Alzheimer's also has its adherents in pathophysiology with numerous citations of Wang X, Zhu X's "*Insights into amyloid-β-induced mitochondrial dysfunction in Alzheimer's disease*" (Abraha et al. 2000). Furthermore, Nunn et al. (2016) offer a solid overview of the quantum influence on mitochondria. In bacterial light-harvesting complexes, quantum tunneling beating is described, effectively representing a coherent superposition of electronic states, equivalent to a nuclear wave packet in the vibrational domain (Wang et al., 2007). This also provides a mechanism for understanding that neurodegenerative diseases like Alzheimer's dementia may be caused by the deterioration of "*Brain Quantum Coherence*" caused by microtubular deterioration, hyperphosphorylation of Tau from chronic spirochete inflammation (Nunn et al., 2016), altered Ca^{2+} signaling, mitochondrial deficiencies, and aberrant processing and polymerization of normally soluble proteins. Due to genetic mutation, external factors, or aging, soluble neuronal proteins assume altered conformations and aggregate, resulting in abnormal neuronal functions and loss (Miklossy, 2008, Collins-Praiano & Corrigan, 2017; Tiwari et al., 2019; Nichols, 2014) and this is why photobiomodulation, which provides photonic therapy from transcranial LED light, is a very promising modality in our search for an AD cure. In our recent review we published the results of placebo-controlled clinical trials, which achieved statistical significance in executive functioning and clock drawing in early to mid-dementia Alzheimer's patients in a two-month therapeutic period (Berman & Nichols, 2019**)**.

List of abbreviations

Aβ -amyloid-β protein

ABP- Actin Binding Protein

AC-alternating current

AD- Alzheimer's disease

ADF- Actin-depolymerization factor

APP- Amyloid-beta precursor

AT8- Phospho-Tau (Ser202, Thr205) Monoclonal Antibody

BDNF- Brain Derived Neurotrophic Factor

CB1- cannabinoid receptor 1

EOAD-early onset dementia

GABA- Gamma-aminobutyric acid

H&E- hematoxylin and eosin

LED-light-emitting diode

LIMK1- LIM domain kinase 1

LLLT-low level laser therapy

LOAD-Late Onset Alzheimer's Dementia

LTP-long term potentiation

MAP-microtubule associated protein

MRI- magnetic resonance imaging

MT-microtubule

NFT- neurofibrillary tangles

NIR-near-infrared

NMDA- N-methyl-D-aspartate

Orch OR- Orchestrated Objective Reduction

PBM- photobiomodulation

PBMT- PBM therapy

PDPK - Proline Directed Protein Kinases

PET – positron emission tomography

PK-protein kinases

PS1- Presenilin-1

siRNA- Small interfering RNA

QD- Quantum Decoherence

TNF- Tumor necrosis factor

tPBM- transcranial photobiomodulation

TPK- Tyrosine Protein Kinases

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