

The Role of Tau Protein on Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is currently a major global health issue that could induce several cognitive and mental problems in early-stage patients, and dementia in varying degrees, even death, in middle and late-stage patients. The formation of beta-amyloid (A-beta) plaque in neurons and the pathological accumulation of tau protein are the two well-known ideas that explain the process of AD. This essay has concluded some research achievements in the past decade, including some important mechanisms (regarding some specific molecules like APOE4 and PyK2) of tau pathologies in AD, several influences on animal and cell models, as well as methods for detection of neuronal tau accumulation in physical and biological fields. The possible therapies with mirodenafil and melatonin were also introduced. In the future, the creation and combination of more new technology, such as real-time monitoring and imaging technology, as well as the clinical discovery of new effects of some drugs on AD patients would help the research and remedies of AD make a progress.

Keywords: alzheimer's disease, tau protein, mechanism, detection methods, therapy.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that can cause the death of brain cells, with brain atrophy being a result. It is common to be seen in dementia patients who suffer from decrement in behavioral skills including socialization and thinking, and these people would possibly become dependent, and even face the threat of death eventually. In terms of the symptoms, it can be separated into three stages according to the extent of this disease. In the relatively early stage, slowness becomes the most apparent symptom, which indicates that patients show memory loss to both familiar people and the surroundings, for example, they would usually forget the original places of a certain item, repeat the same question many times without the answer coming into their mind, and show bluntness dealing with simple tasks in their daily life. At this time their relatives could realize that they are gradually suffering from Alzheimer's disease. If patients do not receive effective treatment in time, the former symptoms would be followed by more serious middle-stage symptoms. As for the judgment of orientation and distances, they may have difficulty distinguishing the locations of distinct places, even their own houses. In addition to this, their mind would also become complex. Patients would be more emotional, indicating that their mood switches among different sorts of negative feelings with trouble in releasing them orally and actively such as depression, anxiety, and confusion, which can harm their sleeping quality, thus triggering a disadvantageous circulation in their mind. The last stage of symptoms is called later symptoms, in which limited mobility and significant loss of verbal ability, weight, and memory could be witnessed so that patients would be almost disabled finally. Many triggers cause this disease. One of the widely known theories is plaques, which are formed by beta-amyloid (A-beta), gathering in the extracellular matrix between neurons. The other one is sedimentary of the tau protein in the microtubes of neurons. Apart from these, the risk of AD also varies between people of different ages, genetics, and lifestyles.

Tau protein is a kind of microtubule-related protein that occupies the largest percentage. It is a major soluble and unfolded protein found in nerve cells, which can bind with microtubes to promote aggregation of microtubule proteins so that they can form bunches, which would be relatively stable in the central nervous system. When it comes to tau pathology, it is well studied that in neurons or gliocyte, the abnormal aggregation of tau acts as the trigger of neurodegenerative disease. After tau protein was generated, it experiences posttranslational modification (PTM), which includes several biochemical procedures like ubiquitination, oxidation, and phosphorylation, which is best studied among them. Though tau bind microtubes with microtubule-binding domains, one of the significant

effects on binding status are the phosphorylation condition of tau. Tau protein contains phosphate groups, with two to three being found in tau protein in healthy brain cells, and five to nine in neurons from AD patients, which is considered as over-phosphorylated. This kind of aberrant tau does not have the necessary biological activity, and it only has very weak strength to bind with microtubules, which is approximately ten percent of that in normal tau. Even the phosphorylation out of the microtubule-binding domain could make a difference in the affinity of tau on microtubules. In addition to phosphorylation, other wrong PTMs can also contribute to tau protein disease, and a large part of these can form neurofibrillary tangles (NFTs), which destroy nerve cells. Some pathological tau also has prion protein-like properties, indicating that they are capable of affecting normal brain cells by translocating from one cell to the other.

This essay will discuss some important mechanisms of tau protein in the cell and animal models, as well as some influences on human bodies which are triggered by tau pathology and AD, after which some biological and physical methods for the detection of AD and some possible therapies are also introduced.

2. Some Important Mechanisms

2.1. The Essence of the Influence of APOE4 on P-Tau Pathology for AD

Human cerebral organoids (hCOs) act as vital vitro models for researching neurological disorders. In hCOs, astrocytic differentiation shows a slower trend than that in neuronal differentiation [1]. Chimeric hCOs (chCOs) were generated by expressing astrogenic two factors, NIFB and SOX9, in order to normalize the maturation of the model so that the effect of APOE4 on p-tau pathologies can be well accessed [2]. In fact, when modeling AD, the chCOs showed a more promoted level of pathologies related to diseases, as an increase of the level of lipid droplets, A-beta, and p-tau were shown in the experiments [2]. A higher neuronal cholesterol level was observed in different chCOs, meaning that the APOE4 in astrocytic cells aggravated the lipid burden in cells [2]. Additionally, APOE4 is essential for the enlargement of p-tau levels in neurons in chCOs [1]. APOE4, which enhances cholesterol levels in neurons, may induce tau pathology as the redundant cholesterol is linked with A-beta and tau pathologies in AD.

2.2. The Protein Pyk2 Restrains P-Tau Formation

The influence that Pyk2 can have on tau pathology was also studied on cultured HEK293T cells [3]. In vitro overexpression system. GSK3 β , which is a kinase, can be activated by Pyk2, and phosphorylate tau [4]. Compared with using other kinases such as Fyn alone, the cooperation of Pyk2 and GSK3 β was the most efficient in enhancing tau phosphorylation, and this system has its ceiling according to different conditions [3]. Significantly, the experiments also showed that the increase in tau phosphorylation was not strictly related to the activity of GSK3 β , indicating that there exists a GSK3 β -independent mechanism, in which the basal Pyk2 level could suppress tau phosphorylation [3]. In addition, the expression of Pyk2 protects tau pathology in vivo [4]. Pyk2 is capable of suppressing tau pathology specifically by influencing tau phosphorylation, instead of functioning on the whole tau expression in neurons [3]. Pyk2 is also protective against some phenotypes resulting from tau phosphorylation, with PS19 transgenic mice being used as models [5]. These mice were suffering from tauopathy and overexpressed human tau protein [5]. The mice with Pyk2 expression had a longer lifespan and better memory that were impaired after being hurt by tau overexpression, compared with those with the Pyk2 gene being deleted [3]. This suggests that Pyk2 expression is capable of improving memory and helping to avoid early death that is induced by tau overexpression. This was further verified by suggesting that Pyk2 can repair synaptic damage in PS19 transgenic mice [3].

2.3. The Function of Mitophagy in Inhibiting Tau Pathology and Improving Cognitive Levels in AD

Mitophagy plays an important role in inhibiting neuronal diseases by preserving healthy neuronal function and survival [6]. However, in neurons of AD patients, their mitophagy is defective, which means that dysfunctional organs and other chemicals could accumulate, creating a burden, even toxic components for cells. This damage could be recovered and thus alleviate the cognitive decline and was verified in *C. elegans* models of AD [6]. Urolithin A (UA), as well as actinonin (AC), are two neuronal mitophagy-inducing agents that were used in models to increase the expression level of many mitophagy-related proteins *in vivo*, and the results showed that mitophagy was enhanced in these models, and the tau phosphorylation was also inhibited in many sites of the gene [6]. This study suggests that pharmacological stimulation of mitophagy could alleviate the damage that resulted from AD in animal models [6]. Additionally, amyloid precursor protein (APP) on mitochondrial membrane channels can block the nuclear-encoded mitochondrial proteins [6]. In APP/PS1 transgenic AD mice, the restoration of mitophagy could also improve some AD phenotypes [6]. These mice were also treated with UA and AC. Their reactive oxygen species (ROS) levels were improved, and the cognitive deficits were also reversed to some extent, as well as synaptic maintenance was also detected, indicating that normal mitophagy has a positive effect on neuronal function [6]. Healthy mitophagy is also able to relieve neuroinflammation [7]. In the microglia culture system, UA and AC can decrease the levels of some vital proinflammatory cytokines like tumor necrosis factor α (TNF α) [7]. Interleukin 10 (IL10) is an anti-inflammatory cytokine, and it was found four times more in UA-treated mice, suggesting the effect that mitophagy has on relieving neuroinflammation [6].

3. Influences On Animal And Cell Models

3.1. Accumulation of Tau Discourages the Conformation of Autophagosome

In HEK293T cells, the effect of the accumulation of tau was detected by measuring microtubule-associated protein light chain 3 (LC3) expression level. LC3 acts as the autophagy marker. Tau5, which is an antibody of tau proteins, firstly detected an increment in its level, indicating that there existed overexpression of tau [8]. This means tau overexpression triggered the dysfunction of autophagy. At the same time, the LC3 II protein level was also decreased, which was measured by immunofluorescence staining [8]. In primary hippocampal neuron cells with Lenti-eGFP-P2A-tau overexpression, a decline of autophagosome formation was witnessed [8]. This is because of the decrease of two components, autophagy-activating kinase 1 (ULK1) and autophagy protein 13 (ATG13), which are responsible for making autophagosomes [9]. Furthermore, the mammalian target of rapamycin kinase complex 1 (mTORC1) functions in a vital upstream pathway of autophagy, whose activity can be regulated by tau overexpression [8]. Tau overexpression upregulates the amino acid pathway by increasing the levels of leucine, glutamic acid, alanine, and glycine, which continuously raises the level of anti-lysosome-associated membrane glycoprotein 1 (LAMP1) and mammalian target of rapamycin (mTOR) [10], by which the mTORC1 pathway can be activated, and autophagosome formation decreased remarkably [10]. To be more specific, tau could bind T cell intracellular antigen 1 (TIA1) with the N-terminal, thus an increased TIA1 level could be seen in the cytoplasm under the effect of tau overexpression, which could lead to the activation of amino acid and mTORC1 pathways [9]. The complement of the prion-related domain of T cell intracellular antigen 1 (TIA1-PRD) can mitigate the dysfunction of autophagy triggered by overexpression of tau [8].

3.2. Hyperexcitability

A huge number of people suffering from AD would finally become demented, while before this symptom takes place, neuronal hyperexcitability can be detected with noninvasive methods [11]. If a neuron has a higher possibility to be stimulated by a certain stimulus, this neuron is thought to be hyperexcited. For early-stage AD patients, it is not at a certain time that their neurons show

hyperexcitability, but the whole neuronal network, even the brain, is suffering from hyperexcitability all the time [12]. This can be detected when the patients are completing the memory-encoding task, as the action potential firing was detected at a higher frequency with a lower firing threshold [11]. Using animal and cell models, it can be seen that hyperexcitability in different brain regions reflects distinct stages of AD [13]. This was explained by selective vulnerability, where the reactions of certain neurons vary in different types of stimulation, and the change would also spread into less vulnerable areas in the brain, leading to a wider zone of neuronal network suffering from this pathological phenomenon [13]. For cell models, induced pluripotent stem cells (iPSCs) were chosen for study because of their clear genetic background [11]. The aggregation of hyper p-tau proteins causes dementia of distinct degrees in brain cells. Tau may also cause hyperexcitability. For example, mutations in the gene encoding tau (MAPT) result in frontotemporal dementia [12]. The decline of tau is protective against hyperexcitability in animal AD models in which the N-methyl-D-aspartate receptors (NMDAR) dysfunction can be reversed so that the negative cycle where tau accumulation aggravates AD is possible to be halted [11]. This could be realized by knocking out the tau proteins to improve the microenvironment in the hippocampus [12]. Tau protein can cause various effects on the excitability of brain cells taking brain regions, phosphorylation status, as well as mutations like MAPT, into consideration [13]. Tau may also cause hyperexcitability, but this needs to be proved by further studies.

4. Methods For Detection Of Ad

4.1. Biological Methods

1) *CSF Biomarkers*: In cerebrospinal fluid (CSF), there are many biomarkers that can be used to measure the extent of AD, such as A-beta, p-tau, total tau (t-tau), and neurofilament light chain (NfL) [14]. CSF levels of tau are proven to be higher in AD patients than that in healthy people [15]. It was witnessed that synaptic biomarkers could significantly distinguish AD patients and non-AD neurologic disorders [14]. The possible relationships between p-tau proteins and some AD symptoms such as dementia were verified by analyzing distinct CSF p-tau levels [15]. Other symptoms that are involved in AD-like synaptic dysfunction and axonal damage can also be measured within CSF [15]. For example, in the preclinical stage, levels of synaptic biomarkers increased remarkably in older individuals with higher brain metabolism, indicating that the investigation through biomarkers in CSF is efficient [14]. To summarize, CSF biomarkers can act as measurement indexes to support targeted research of tau pathology.

2) *Serum and Plasma P-Tau*: It is suggested that p-tau measurements can be placed emphasis on serum samples rather than other blood parts as the measurement of p-tau protein level has already been added into anti-amyloid trial programs, and other biomarkers in serum are also considered worth to be tested [16]. Serum and plasma samples should also be used separately, and the concentrations of biomarkers should not be interchanged within these two kinds of samples [16]. Both p-tau 231 and 181 in serum and plasma samples could be measured to distinguish AD patients and non-AD patients, and these results also had significant correlation with those that were diagnosed from CSF biomarkers, indicating that p-tau biomarkers in serum and plasma could be considered as an efficient method to support clinical works [16].

4.2. Physical Methods

1) *Positron emission tomography*: Positron emission tomography (PET) is a completely quantitative and accurate technique that can be used to create images to exhibit tau pathology efficiently. However, because of the limited spatial resolution of PET scanners, the tau density, and spatial distribution should reach a sufficient level so that PET imaging could be used efficiently to detect tau protein [17]. In the early stages of tau pathology, only scanning by PET cannot get enough evidence to show that tau does not spread in the brain, because tau usually does not accumulate at a condensed degree at this stage, however, as time goes by, tau has a great density which can satisfy the signal-to-noise ratio for PET working, but the illness has also aggravated at this time [17]. Thus,

it is vital to combine further validation with this technique and use PET to execute continuous detection rather than periodical tasks [17]. In this way, the progress of tau pathology could be well learned by recording continuous tau accumulation, and in view of the above new therapeutic methods may be developed.

2) *Machine Learning*: Future toxic tau protein accumulation can be predicted by combining multimodal biological data with machine learning [18]. This plays a significant role in reducing sample size and detecting remarkable changes in tau density [18]. To be more specific, the CSF biomarkers like APOE4 and NfL, as discussed above, could be quantified to assess the stage where tau accumulation has already reached [18]. By training machines to learn and assess diverse relationships from various biomarkers and models (for example, patients in different stages of AD), the prognostic index could be figured out by this approach, which helps anticipate the track of tau pathologic accumulation in asymptomatic and mild symptomatic samples [18]. In this way, patients can be separated into different groups for clinical treatments according to the tau accumulation tracks which have been predicted by the prognostic index, and they could also receive continuous detection by combining other methods with the predicted data.

5. Possible Therapies In The Future

5.1. Mirodenafil

Mirodenafil acts as phosphodiesterase 5 inhibitor, which has a variety of functions such as reducing p-tau burden, inhibiting apoptosis, and impeding several pathways to reduce pathological tau accumulation [19]. In the transgenic AD mice model, mice treated with mirodenafil got a 64%-time decline and a 44% distance decrease compared with mice with AD but without any treatment in water maze training, indicating the potential of mirodenafil in improving the cognitive ability in AD patients [19]. By shielding mitochondrial membrane potential, mirodenafil can also prevent neuronal unnatural death. It has been reported that mitochondrial depolarization enhances apoptosis in neurons [6]. Combined treatment with mirodenafil showed the ability to remarkably reduce the concentration of apoptotic markers like caspase-3, by which the neuronal survival rate raised compared with treating with A-beta42 alone [19]. The p-tau burden was also decreased by 16% [19]. Moreover, hydrogen peroxide-induced calcium ion spike in cells was remarkably decreased by treating with mirodenafil, which is also a meaningful discovery as the hydrogen peroxide is responsible for rising intracellular calcium ion levels that could induce contraction of brain pericytes [19].

5.2. Melatonin

The experiment used transgenic mice model which could overexpress p-tau in their bodies. Their pathology and symptom also vary from age to age [20]. The mice were treated with saline and melatonin, and the result showed that the p-tau level in hippocampi and cortices decreased significantly in groups treated with melatonin [21]. This effect could be seen in both early and middle stages of tau pathology, and it also works in decreasing p-tau and t-tau levels [20]. In addition, melatonin could also alleviate tau pathology by regulating miRNA expression [21]. More importantly, melatonin could inhibit p39, an activator of tau kinase cyclin-dependent kinase 5 (CDK5), via miR-504-3p, because miR-504-3p was demonstrated to target p39 at 3'UTR [21]. Transgenic mice that were treated with melatonin witnessed a significant decline in p39 expression level, and by transfecting with miR-504-3p inhibitor, the p39 expression was higher than that in the control group [21]. This is because miR-504-3p is capable of prohibiting mRNA expression of p39 so that the p39 expression could be downregulated [21]. To summarize, melatonin is able to induce the upgradation of miR-504-3p, which could silence p39 to inhibit pathological tau phosphorylation.

6. Conclusion

In conclusion, this essay firstly introduced the basic background symptoms in different stages of AD, as well as some widely known theories about the triggers of AD, which included some basic properties of tau protein. Then some vital molecular mechanisms which could reveal the role of tau in AD, as well as some influences on animal and cell models were introduced. Finally, the detection methods in terms of biology and physics, and some possible therapies were provided. One of the important causes of AD is the pathological accumulation of p-tau and tau hyperphosphorylation. There are many mechanisms revealing the detriment of tau accumulation, such as APOE4 can induce tau pathology via raising cholesterol levels in neurons, the expression of Pyk2 is capable of repairing the damage in neural cells and improving the cognitive levels of AD patients, and mitophagy has the ability to relieve neuroinflammation so that AD phenotype could be alleviated. The abnormal increase in p-tau concentration in neurons would result in hyperexcitability, and its overexpression impedes the formation of autophagosome, which could disturb the normal operation of autophagy so that p-tau will become more condensed as it cannot be degraded, which finally creates a negative circulation. There are many ways to detect AD and tau distribution in brain cells, which varies within biological (CSF biomarkers and serum tau samples) and physical fields (PET and machine learning). For potential treatments, mirodenafil and melatonin may have the potential to contribute to AD therapy as they were currently verified to be efficient in reducing the tax burden and improving the intracellular microenvironment. Nowadays, it is still difficult to find out the most efficient way to cure AD patients and repair their cognitive defects, as many molecular mechanisms still remain unknown. Neurological dysfunction is largely irreversible, which indicates the difficulty in finding the possible therapies for AD, and many solutions now are provided to be inefficient or too strong. Many medical ways can just remit the symptoms but cannot act as radical cures. Thus, it is of great importance for the elderly to have health examinations regularly and receive targeted treatments in time. If more novel and efficient real-time monitoring technology could be invented and combined into the study and treatment, it is beneficial for impelling the research progress of AD and related pathologies.

References

- [1] H. Song et al. (2002) 'Astroglia induce neurogenesis from adult neural stem cells', *Nature*, 417 (6884), pp. 39 - 44.
- [2] S. Huang et al. (2022) 'Chimeric cerebral organoids reveal the essentials of neuronal and astrocytic APOE4 for Alzheimer's tau pathology', *Signal Transduction and Targeted Therapy*, 7 (1), pp. 1 - 10.
- [3] A. H. Brody et al. (2022) 'Alzheimer risk gene product Pyk2 suppresses tau phosphorylation and phenotypic effects of tauopathy', *Molecular Neurodegeneration*, 17 (1), pp. 1 – 33.
- [4] C. Li et al. (2018) 'Pyk2 is a Novel Tau Tyrosine Kinase that is Regulated by the Tyrosine Kinase Fyn.' *Journal of Alzheimer's Disease*, 64 (1), pp. 205 - 221.
- [5] Y. Yoshiyama et al. (2007) 'Synapse Loss and Microglial Activation Precede Tangles in a P301S Tauopathy Mouse Model', *Neuron*, 54 (2), pp. 343 - 344.
- [6] E. F. Fang et al. (2019) 'Mitophagy inhibits amyloid- β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease', *Nature Neuroscience*, 22 (3), pp. 401 – 412.
- [7] H. Keren-Shaul et al. (2017) 'A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease.' *Cell*, 169 (7), pp. 1276 - 1290.
- [8] M. Li et al. (2022) 'Intracellular accumulation of tau inhibits autophagosome formation by activating TIA1 amino acid mTORC1 signaling', *Military Medical Research*, pp. 1 – 16.
- [9] X. Li et al. (2005) 'Levels of mTOR and its downstream targets 4E-BP1, eEF2, and eEF2 kinase in relationships with tau in Alzheimer's disease brain', *FEBS Journal*, 272 (16), pp. 4211 – 4220.
- [10] I. G. Ganley et al. (no date) 'ULK1. ATG13. FIP200 complex mediates mTOR signaling and is essential for autophagy', *Journal of Biological Chemistry*, 284 (18), pp.12297 - 12305.

- [11] H. T. D. Anastacio et al. (2022) 'Neuronal hyperexcitability in Alzheimer's disease: what are the drivers behind this aberrant phenotype?', *Translational Psychiatry*, 12 (1), pp. 1 - 14.
- [12] A. J. Beagle et al. (2017) 'Relative Incidence of Seizures and Myoclonus in Alzheimer's Disease, Dementia with Lewy Bodies, and Frontotemporal Dementia', *Journal of Alzheimer's disease: JAD*, 60 (1), pp. 211 – 223.
- [13] M. A. Busche et al. (2012) 'Critical role of soluble amyloid-beta for early hippocampal hyperactivity in a mouse model of Alzheimer's disease', *Proceedings of the National Academy of Sciences of the United States of America*, 109 (22), pp. 8740 - 8745.
- [14] M. A. Marta et al. (2021) 'CSF Synaptic Biomarkers in the Preclinical Stage of Alzheimer Disease and Their Association with MRI and PET A Cross-sectional Study.', *Neurology*, 97 (21), pp. 2065 - 2078.
- [15] K. E. J. Wesenhagen et al. (2022) 'P-tau subgroups in AD relate to distinct amyloid production and synaptic integrity profiles.', *Alzheimer's research & therapy*, 14 (1), p. 95.
- [16] P. R. Kac et al. (2022) 'Diagnostic value of serum versus plasma phospho-tau for Alzheimer's disease', *Alzheimer's Research and Therapy*, 14 (1), pp. 1 – 12.
- [17] A. Moscoso et al. (2022) 'Imaging tau pathology in Alzheimer's disease with positron emission tomography: lessons learned from imaging-neuropathology validation studies', *Molecular Neurodegeneration*, 17 (1), pp. 1 – 5.
- [18] J. Giorgio et al. (2022) 'A robust and interpretable machine learning approach using multimodal biological data to predict future pathological tau accumulation', *Nature Communications*, 13 (1), pp. 1 – 14.
- [19] B. W. Kang et al. (2022) 'Phosphodiesterase 5 inhibitor mirodenafil ameliorates Alzheimer-like pathology and symptoms by multimodal actions.', *Alzheimer's research & therapy*, 14 (1), p. 92.
- [20] C. Andorfer et al. (2003) 'Hyperphosphorylation and aggregation of tau in mice expressing normal human tau isoforms.', *Journal of Neurochemistry*, 86 (3), pp.582 - 590.
- [21] D. Chen et al. (2022) 'Melatonin ameliorates tau-related pathology via the miR-504-3p and CDK5 axis in Alzheimer's disease', *Translational Neurodegeneration*, 11 (1), pp. 1 – 19.