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Tauopathies Support

Product Information Sheet

Tauopathies are a group of neurodegenerative diseases associated with the pathological aggregation of tau protein in the human brain. Tau is a microtubule-associated protein that plays a crucial role in stabilizing microtubules in nerve cells, which are important for proper neuronal function and for the transport of nutrients and other cellular components. In tauopathies, tau proteins become abnormally phosphorylated and form neurofibrillary tangles, leading to cell death and dysfunction in the brain.

The tau protein is primarily associated with microtubule stability in neurons, but it has multiple functions that could contribute to neurodegenerative processes when dysregulated. These functions include axonal transport, cell signaling, and possibly even cell secretion processes. Abnormalities in tau, such as hyperphosphorylation and misfolding, lead to the formation of neurofibrillary tangles, which are hallmarks of these conditions.

The clinical presentation of tauopathies can vary significantly, reflecting the broad spectrum of underlying pathologies. Patients may experience cognitive decline, behavioral changes, movement disorders, and language impairment. Overlap of symptoms is common, challenging the classification into discrete syndromes.

Primary tauopathies include conditions such as Alzheimer's disease (AD), which is the most common form of dementia, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease, and others. Secondary tauopathies are those where tau pathology exists alongside other primary neurodegenerative processes.

Research into tau therapeutic strategies has been growing, as it's clear that targeting tau pathology could be key to treating these diseases. Current therapeutic strategies are focused on mitigating the formation and spread of tau aggregates and understanding the role of tau in disease progression. Studies have shown that neurofibrillary tangles correlate strongly with cognitive decline, and the anatomical distribution of tau aligns with clinical signs of AD and other tauopathies.

Common Tauopathies

1. **Alzheimer's Disease (AD)**: The most prevalent tauopathy, characterized by the presence of both beta-amyloid plaques and neurofibrillary tangles.
2. **Pick's Disease**: Features severe frontal lobe atrophy and is marked by rounded tau protein inclusions called Pick bodies.
3. **Progressive Supranuclear Palsy (PSP)**: Known for tau accumulations in brainstem and basal ganglia, causing movement disorders, dementia, and eye movement abnormalities.
4. **Corticobasal Degeneration (CBD)**: Characterized by neuronal loss, gliosis, and tau deposits in the cerebral cortex and basal ganglia.

Treatment Perspectives

There are currently no cures for tauopathies, and treatments mainly focus on managing symptoms. However, several experimental approaches aim at reducing tau pathology. These include anti-tau antibodies, tau aggregation inhibitors, and strategies to reduce tau phosphorylation or promote tau clearance. In many neurodegenerative diseases, mutations and other cellular events alter the normal folding process, and the misfolded proteins begin to accumulate. The accumulation of tau is thought to disrupt normal cellular function and lead to the death of neurons. Due to its misfolded state being a consistent component of so many incurable neurodegenerative diseases,

Phytotherapeutic interventions that rescue pathological tau dysfunction, such as targeting aberrant tau hyperphosphorylation, modulating proteostasis mechanisms, or modulating tau protein translation, hold promise as disease modifying therapies for tauopathies.

Phytotherapeutic Formulations

Some phytotherapeutic formulations are investigated for their neuroprotective effects, potentially beneficial for tauopathies. We are developing a formulation that we believe will address the tauopathies, the ingredients include the following:

1. **Huperzine A**: Derived from the Chinese club moss Huperzia serrata, it has been shown to improve cognitive function in Alzheimer's patients by increasing neurotransmitter levels. Huperzine A, is suggested to ameliorate memory and learning defects in patients with AD.
2. **Glycyrrhiza glaba:** has the effects of reducing tau misfolding and reactive oxygen species (ROS) and regulating the expressions of UPR pathway-related genes. These findings indicate the potential role of G. glaba as a novel herb medication for the treatment of AD and tauopathies.
3. **Ginkgo Biloba**: Contains flavonoids and terpenoids that have antioxidant and anti-inflammatory properties. Studies suggest it may help improve cognitive function and daily living activities in mild Alzheimer's disease.
4. **Curcumin**: Found in turmeric, curcumin has anti-inflammatory and antioxidant properties. It's thought to reduce oxidative stress and amyloid pathology in Alzheimer's disease.
5. **Green Tea (Epigallocatechin Gallate, EGCG)**: The polyphenols in green tea may help to stabilize tau proteins and reduce their misfolding, as shown in some preclinical studies.
6. **Lion's Mane Mushroom (Hericium erinaceus)**: Has been shown to stimulate nerve growth factor synthesis, potentially aiding in the protection and repair of nerve cells.
7. **Bacopa monnieri**: An herb traditionally used in Ayurvedic medicine that has shown potential in improving memory and reducing oxidative stress in neurological disorders.

The research into tauopathies and their treatment using herbal analogs of efficacious compounds is still relatively nascent. However, several promising herbal components have shown potential in preclinical studies. When discussing the development of herbal formulations for tauopathies, it's important to focus on the mechanisms through which these compounds may exert neuroprotective effects, such as anti-inflammatory actions, antioxidant properties, inhibition of tau aggregation, and modulation of tau phosphorylation.

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REVIEW Open Access

A walk through tau therapeutic strategies

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Abstract

Tau neuronal and glial pathologies drive the clinical presentation of Alzheimer's disease and related human tauopathies. There is a growing body of evidence indicating that pathological tau species can travel from cell to cell and spread the pathology through the brain. Throughout the last decade, physiological and pathological tau have become attractive targets for AD therapies. Several therapeutic approaches have been proposed, including the inhibition of protein kinases or protein-3-O-(N-acetyl-beta-D-glucosaminyl)-L-serine/threonine Nacetylglucosaminyl hydrolase, the inhibition of tau aggregation, active and passive immunotherapies, and tau silencing by antisense oligonucleotides. New tau therapeutics, across the board, have demonstrated the ability to prevent or reduce tau lesions and improve either cognitive or motor impairment in a variety of animal models developing neurofibrillary pathology. The most advanced strategy for the treatment of human tauopathies remains immunotherapy, which has already reached the clinical stage of drug development. Tau vaccines or humanised antibodies target a variety of tau species either in the intracellular or extracellular spaces. Some of them recognise the amino-terminus or carboxy-terminus, while others display binding abilities to the proline-rich area or microtubule binding domains. The main therapeutic foci in existing clinical trials are on Alzheimer's disease, progressive supranuclear palsy and non-fluent primary progressive aphasia. Tau therapy offers a new hope for the treatment of many fatal brain disorders. First efficacy data from clinical trials will be available by the end of this decade.

Keywords: Alzheimer's disease, Tau vaccines, Therapeutic interventions, Immunotherapy, Tauopathies, PET imaging, Aggregation

Introduction

Tau protein is considered to be one of the most peculiar proteins in the central nervous system. It is located in several cell compartments, including the axon, dendrites, nucleus, nucleolus, cell membrane and synapses [310]. However, tau is also present in the interstitial fluid [284, 370], and can pass into cerebrospinal fluid (CSF), where it is found at concentrations of 10-25 pg/ml (pT181-tau) or 300-400 pg/ml (tau) [28, 29, 248]. In physiological conditions, extracellular tau may enter neurons either via a dynamin-mediated endocytic mechanism or by classical endocytosis [95]. In neurodegenerative tauopathy, diseased modified tau can propagate along neuroanatomically connected brain areas via multiple mechanisms and spread tau pathology throughout the brain [231].

Tau belongs to the group of natively disordered proteins, which exist in a highly flexible, unfolded structural state, largely devoid of well-defined secondary and tertiary structure, although they are able to fold after binding to targets [329]. The highly flexible structure of tau protein allows interaction with multiple partners, suggesting its involvement in numerous signalling pathways [308]. The dark side of its structural repertoire is its ability to interact with other tau molecules to form oligomers and filaments [298, 338, 339]. These complexes cause degeneration of neurons and glial cells [97], manifesting as a group of neurodegenerative disorders termed 'tauopathies' [312].

The most prominent tauopathy is Alzheimer's disease (AD), the common cause of dementia in older adults. AD is an incurable, progressive degenerative disease of the brain, characterized by the presence of tau and ß- amyloid (Aß) pathology [286]. There are no disease-modifying drugs available for AD; only symptomatic treatments trying to counterbalance the neurotransmitter disturbance exist. No significant new drug for AD has been approved in the last 14 years, despite extensive clinical trials. The pipeline has

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REVIEW

The Role of Traditional Chinese Medicine Natural Products in β-Amyloid Deposition and Tau Protein Hyperphosphorylation in Alzheimer's Disease

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Abstract: Alzheimer's disease is a prevalent form of dementia among elderly individuals and is characterized by irreversible neurodegeneration. Despite extensive research, the exact causes of this complex disease remain unclear. Currently available drugs for Alzheimer's disease treatment are limited in their effectiveness, often targeting a single aspect of the disease and causing significant adverse effects. Moreover, these medications are expensive, placing a heavy burden on patients' families and society as a whole. Natural compounds and extracts offer several advantages, including the ability to target multiple pathways and exhibit high efficiency with minimal toxicity. These attributes make them promising candidates for the prevention and treatment of Alzheimer's disease. In this paper, we provide a summary of the common natural products used in Chinese medicine for different pathogeneses of AD. Our aim is to offer new insights and ideas for the further development of natural products in Chinese medicine and the treatment of AD.

Keywords: Alzheimer's disease, β-amyloid deposition, tau-protein hyperphosphorylation, natural products, Chinese herbal medicine, review

Introduction

Alzheimer's disease (AD) is the most prevalent degenerative disease of the central nervous system in elderly individuals. It has a gradual and progressive onset, leading to cognitive decline, mental and behavioral abnormalities, and a reduced ability to perform daily activities.[1] As the population ages, dementia has become a widespread condition among older individuals, with AD dementia accounting for 60% to 80% of cases. It is also the primary cause of disability and mortality in elderly individuals.[2,3]

China currently has the highest number of dementia patients worldwide.[4] Epidemiological surveys indicate that there are approximately 15.07 million individuals over the age of 60 with dementia in China, with approximately 9.83 million of them diagnosed with AD.[5] This places a significant burden on both the families of the patients and society as a whole. The primary pathological characteristics of AD include the formation of senile plaques (SPs) through the accumulation of extracellular amyloid β-protein (Aβ), the presence of intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated Tau proteins, and synaptic loss.[6] Current treatment for cognitive symptoms primarily involves the use of cholinesterase inhibitors (donepezil, carboplatin, and galantamine) and glutamate receptor antagonists (memantine and memantine combined with cholinesterase inhibitors).[7] However, it is important to note that cholinesterase inhibitors may lead to increased adverse effects, such as skin irritation, weight loss, nausea, and vomiting.[7] On the other hand, glutamate receptor antagonists, particularly memantine, have shown limited effectiveness in the early stages of AD.[7] Atypical antipsychotics can help alleviate psychiatric and behavioral symptoms associated with AD, but there is a risk of

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ORIGINAL RESEARCH

The aqueous extract of *Glycyrrhiza inflata* can upregulate unfolded protein response-mediated chaperones to reduce tau misfolding in cell models of Alzheimer's disease

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Background: Alzheimer's disease (AD) and several neurodegenerative disorders known as tauopathies are characterized by misfolding and aggregation of tau protein. Although several studies have suggested the potential of traditional Chinese medicine (TCM) as treatment for neurodegenerative diseases, the role of TCM in treating AD and tauopathies have not been well explored.

Materials and methods: Tau protein was coupled to the DsRed fluorophore by fusing a pro-aggregation mutant of repeat domain of tau (ΔK280 tau_{RD}) with DsRed. The ΔK280 tau_{RD}-DsRed fusion gene was then used to generate Tet-On 293 and SH-SY5Y cell clones as platforms to test the efficacy of 39 aqueous extracts of TCM in reducing tau misfolding and in neuroprotection.

Results: Seven TCM extracts demonstrated a significant reduction in tau misfolding and reactive oxidative species with low cytotoxicity in the ΔK280 tau_{RD}-DsRed 293 cell model. *Glycyrrhiza inflata* and *Panax ginseng* also demonstrated the potential to improve neurite outgrowth in the ΔK280 tau_{RD}-DsRed SH-SY5Y neuronal cell model. *G. inflata* further rescued the upregulation of *ERN2* (pro-apoptotic) and downregulation of unfolded-protein-response-mediated chaperones *ERP44*, *DNAJC3*, and *SERP1* in ΔK280 tau_{RD}-DsRed 293 cells.

Conclusion: This in vitro study provides evidence that *G. inflata* may be a novel therapeutic for AD and tauopathies. Future applications of *G. inflata* on animal models of AD and tauopathies are warranted to corroborate its effect of reducing misfolding and potential disease modification.

Keywords: Alzheimer's disease, tauopathy, tau misfolding, TCM extracts, *G. inflata*, UPR-mediated chaperones

Introduction

Several neurodegenerative disorders known as tauopathies, such as Alzheimer's disease (AD), frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration, are characterized by abnormal aggregation of tau protein.[1] In these diseases, tau becomes abnormally hyperphosphorylated and misfolded, forming insoluble aggregations.[2] Such misfolded tau proteins are toxic to cells, particularly neurons, and several lines of evidence have shown that these aberrant proteins are responsible for neurodegeneration.[2]

Tau, mainly expressed in neurons, plays an important role in the constitution of neuronal microtubule network by assembling tubulin monomers into microtubules.[3] It also provides links between microtubules and other cytoskeletal components.[4] Under

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