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Review

A New Strategy in Epilepsy Therapy Through Attenuation of Phosphorylated Tau and Amyloid-beta

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Abstract

Epilepsy is a progressive disorder associated with cognitive decline and worsening of other neuropsychiatric comorbidities, as well as the development of drug resistance. Clinical and experimental evidence has shown a link between epilepsy and neurodegenerative pathways such as tau and amyloid-beta (Aβ) proteins. Increased phosphorylation of tau and Aβ is toxic to neurons and can lead to the destabilization of microtubules in the nervous system and axonal dysfunction, resulting in dendrite shrinkage, destabilization of synapses, and ultimately neuronal death. Inhibition or attenuation of tau and Aβ phosphorylation may provide neuroprotective effects and be beneficial in reducing seizures and neurodegeneration. Therefore, anti-amyloid antibodies represent a promising approach, though their use is accompanied by potential benefits and drawbacks. Additionally, anti-tau antibodies hold theoretical potential as an option in epilepsy therapy.

Keywords: Amyloid-beta peptides, epilepsy, neurology, seizure, tau protein

INTRODUCTION

A seizure is a sudden change in nerve function caused by an excessive discharge of neuronal impulses, or an imbalance in excitatory and inhibitory signals that are not well-coordinated in the brain. Epilepsy is a condition in which two or more seizures occur repeatedly without a trigger.[1] The World Health Organization states that epilepsy currently affects approximately 50 million people worldwide, making it one of the most common neurological disorders encountered globally.[2] Some cases of epilepsy that occur after brain injury [such as status epilepticus (SE), traumatic brain injury (TBI), or infection] are known as acquired or post-traumatic epilepsy. Typically, this form of epilepsy occurs after a lag time between the initial injury and seizures of at least 3 months, and sometimes several years.[3] The International League Against Epilepsy (ILAE) classification includes aetiologies of epilepsy such as structural, genetic, infectious, metabolic, immune, and unknown causes. Additionally, The ILAE curriculum introduces another category, which include neurodegenerative.[4] Neurodegeneration is a pathological sign in the brain associated with acquired epilepsy, and the process of neurodegeneration in epileptogenic areas triggers neuroinflammation, tissue reorganization, or molecular changes that can contribute to transforming an initially normal brain into an epileptic one.[5] Ali et al.[6] showed that epilepsy can be a progressive disorder associated with decreased cognitive function, increased neuropsychiatric comorbidities, and the development of drug resistance through pathological mechanisms often described in neurodegenerative conditions. Clinical and experimental studies have shown a correlation between epilepsy and neurodegenerative processes, such as increased levels of tau and amyloid-beta (Aβ) proteins in certain pathways.[5,6] Therefore, this review will focus on the role of Aβ peptide accumulation and tau pathology in epilepsy, as well as explore the potential of anti-amyloid monoclonal antibodies and tau-centric treatments as novel strategies in the management of epilepsy.

Target Intervention in Epilepsy

Seizures are widely understood to result from either excessively enhanced excitatory processes in certain neuronal populations or insufficient neuronal inhibition. Traditionally, this mechanism was attributed to hyperactivity in glutamatergic transmission and a deficiency in γ-aminobutyric acid (GABA) receptor-mediated inhibition. However, emerging evidence highlights the complexity of GABA and glutamate interactions, revealing that both neurotransmitters can play excitatory and inhibitory roles within the central nervous system. In addition to synaptic N-methyl-D-aspartic acid (NMDA) and GABAA receptors, extra-synaptic receptors for these amino acid neurotransmitters have recently been implicated in seizure pathophysiology. Factors such as changes in gene expression, polymorphisms, loss or gain of

function mutations, and cellular energy imbalances can also disrupt the function of ligand- and voltage-dependent sodium, potassium, chloride, and calcium channels, further contributing to seizure activity. Thus, the primary goal of conventional anti-epileptic drugs is to decrease the frequency and severity of seizures by targeting voltage-dependent sodium, potassium, and calcium channels, GABAA receptors, enzymes responsible for GABA metabolism, and GABA transporters.[7]

Despite this, acquired epilepsy exhibits diverse etiologies. A causative epileptogenic brain injury-such as stroke, SE, TBI, or infection-can be identified in a subset of patients. Growing evidence indicates that acquired epilepsy may be a progressive disorder, linked to cognitive decline, worsening neuropsychiatric comorbidities, and the development of pharmacoresistance. During epileptogenesis, a broad range of potentially pro-epileptogenic neurodegenerative changes occurs within limbic structures. These include mossy fiber sprouting, neuronal reorganization with synaptic remodeling, neurogenesis, blood-brain barrier disruption, alterations in GABA receptors and GABAergic neurons, changes in peptide, and brain-derived neurotrophic factor expression, neuroinflammation, ion channel modifications, and disruptions in axonal transport. Additionally, Aβ peptide accumulation, tau pathology, and protein phosphatase 2A (PP2A) dysfunction are observed, along with other cellular and functional changes. While these neuropathological changes are not specific to epilepsy, they closely resemble those found in neurodegenerative disorders such as Alzheimer's disease (AD).[5] Novel therapies targeting neurodegenerative pathways, such as tau, Aβ, mammalian target of rapamycin (mTOR), and neuroinflammation, may hold the potential to serve as anti-epileptic and/or disease-modifying treatments for patients with acquired epilepsy.

Implication of Neurodegeneration-tau and Aβ Proteins in Epilepsy

Investigating the role of Aβ in the context of epilepsy is of critical importance, given several studies supporting a close association between AD and epileptic seizures, potentially sharing common underlying mechanisms. Aβ aggregation into oligomers and fibrils is established as the primary driver of neurotoxicity, with Aβ oligomers-rather than amyloid plaques-being strongly linked to neuronal loss. Aβ exists in two isoforms: Aβ40, which is more abundant, and Aβ42, which is more prone to aggregation and plays a greater role in the disease process.[8] Studies using intracerebroventricular injection of Aβ1-42 have demonstrated its ability to mediate neurodegeneration and induce an AD-like phenotype in animal models and non-human primates.[9] The mechanisms underlying Aβ1-42-induced neurodegeneration include mitochondrial dysfunction, oxidative stress, degeneration of cholinergic neurons, and increased Aβ1-42 deposition, ultimately leading to cell death. Additionally, Aβ regulates NMDA receptors (NMDARs) and disrupts the ionic balance between synaptic and extra-synaptic NMDAR signaling, contributing further to neuronal dysfunction and degeneration.[8]

MAIN POINTS

- A large amount of phosphorylated tau was found in the sclerotic hippocampus, and its presence was statistically significant in relation to seizure frequency.
- Hyperphosphorylation of tau and resulting in microtubule destabilization resulting in axonal and synaptic dysfunction, as well as neurodegeneration.
- Accumulation of amyloid-beta (Aβ) can lead to cognitive dysfunction; abnormal tissue synchronization and resulting in epilepsy.
- Therapies that target the tau and Aβ pathways directly can be beneficial in reducing neurodegeneration and cognitive impairment and reducing seizure duration.

The cascade of events in the development of seizures and tau pathology begins with endogenous tau having a facilitative role in the onset of seizure activity following disease or traumatic insult. This leads to network hyperexcitability, which, in turn, results in cognitive decline and the activation of cellular mechanisms involving mTOR and tau kinases and phosphatases. These mechanisms drive abnormal tau phosphorylation. Overactivation of these signaling pathways promotes pathological tau hyperphosphorylation and aggregation, increasing susceptibility to epilepsy. Furthermore, these pathological changes can contribute to the cognitive decline commonly associated with epilepsy.[10]

Tau and Beta-amyloid Interaction in Neuronal Death

Tau protein occurs naturally in the human brain and has several functions, including the assembly and stabilization of microtubules.[11] Tau has a significant influence on neuronal activity, and models with excessive tau expression show hyperexcitability, which can then induce seizures.[12] In neuronal cells, tau is concentrated in axons; however, a physiological role for tau in dendrites has been described.[13] Tau plays an integral role in the hyperactivity observed in mouse models of SE. Loss of tau may also act as a neuroprotective mechanism, as it may result in impaired localization of postsynaptic fyn kinase, which is involved in cell growth, and reducing damage caused by neuronal overactivity.[14]

In addition to tau overload, patients with therapy-resistant chronic epilepsy show imaging characteristics of brain aging, increased Aβ burden, and accelerated ventricular expansion. Following seizures, surface receptors are activated, which in turn activate the mTOR pathway, causing increased endoplasmic reticulum (ER) and oxidative stress. Chronic activation of cellular stress pathways can result in neuronal death and cognitive impairment. ER stress activates pancreatic eIF2 kinase-like ER kinase (PERK), which then phosphorylates and activates eukaryotic translation initiation factor 2-alpha (eIF2α); inhibiting protein synthesis and triggering neuronal cell death. At the same time, phosphorylated eIF2α inhibits the translation of beta-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) mRNA and enhances the amyloidogenic processing of APP. This processing by BACE1 β-secretase results in the release of soluble APP-β (sAPPβ) and this processing by BACE1 γ-secretase generates the Aβ-42 peptide. In the same way, processing of non-amyloidogenic APP through the enzyme α-disintegrin and metalloproteinase 10 produces the peptides soluble APP-α (sAPPα) and peptide-3. In addition to increasing the expression of neprilysin, an enzyme that plays a role in the clearance of Aβ-42, Aβ-42 also induces mTOR activity, ER stress, and oxidative stress. Ribosomal protein kinase p70S6K, activated by mTOR, increases tau and BACE1 protein synthesis and phosphorylates tau. Cellular stress also activates pro-apoptotic jun N-terminal kinase (JNK) and inhibits the activity of PP2A, which is the major tau phosphatase, leading to decreased tau phosphorylation. In addition, JNK phosphorylates APP and tau

proteins, which can lead to neuronal death and further cognitive impairment (Figure 1).[15] The ER stress response also increases their capacity for phagocytosis and the breakdown of tau.[16] Polanco et al.[17] showed that Aβ and tau interact in many neural compartments, including:

- In dendrites, Aβ facilitates the assembly of a postsynaptic excitotoxic signaling complex consisting of NMDARs and postsynaptic density protein 95 through several tau-dependent signaling cascades;

- Tau-mediated excitotoxicity and microtubule damage interact with the potential for long-term Aβ-induced disruption to cause synaptic damage;

- In addition, Aβ and tau interact synergistically to impair mitochondrial function and disrupt neuronal energy homeostasis.

Increased Phosphorylated Tau and Beta-amyloid in Epilepsy

Many recent clinical and experimental studies have shown evidence of an association between neurodegenerative markers such as the accumulation of phosphorylated tau[18] and beta amyloid[19] and mesial temporal lobe epilepsy (TLE),[20,21] drug-resistant epilepsy,[22] TLE,[23] drug-resistant TLE,[15] and generalized SE.[21] In a study conducted by Toscano et al.,[20] a large amount of phosphorylated tau was found in the sclerotic hippocampus, with this finding being statistically significant in its association with seizure frequency. However, in a study conducted by Aroor et al.,[22] there was no statistically significant correlation between p-tau and/or Aβ pathology and full-scale intelligence quotient and epilepsy duration despite there being an increase in phosphorylated tau associated with neutrophil threads, neurofibrillary tangles (NFT) and Aβ accumulation. Gourmaud et al.[15] showed that tau and amyloid found in drug-resistant TLE are associated with neurodegeneration, which is the basis of cognitive impairment in patients with epilepsy. Therefore, therapies that target the tau and Aβ pathways directly can be beneficial in reducing neurodegeneration and cognitive impairment,[13] and reducing seizure duration.[15]

Role of Phosphorylated Tau in Epilepsy

Under normal physiological conditions, the tau protein exists in a balance between binding and unbinding from the microtubules. This balance is regulated by the level of partial phosphorylation of tau, which is controlled by kinases and phosphatases that maintain microtubule stability. However, in pathological states, this balance is disrupted, causing hyperphosphorylation of tau and resulting in microtubule destabilization. An abnormal increase in tau phosphorylation can reduce its binding to microtubules, resulting in the destabilization of the cytoskeleton in the central nervous system. Pathologically, phosphorylated tau detaches from microtubules and forms aggregates called NFTs, which accumulate within neurons, astrocytes, and oligodendroglia, resulting in axonal and synaptic dysfunction, as well as neurodegeneration. A tau phosphatase enzyme, PP2A, supports tau-mediated microtubule stabilization and prevents NFT formation and aggregation of phosphorylated tau. Sodium selenate (Na_2SeO_4) increases PP2A activity. Treatment with sodium selenate for three months significantly reduces the phosphorylation levels of tau at the AT180 site and total tau in the hippocampus and amygdala of the model group compared to the control group. Treatment with sodium selenate significantly reduces the frequency and duration of seizures in animal models of epilepsy.[3]

Role of Amyloid-beta in Epilepsy

Aβ results from the breakdown of the APP by a group of enzymes, including α-secretase, β-secretase, and γ-secretase. Aβ then assembles into dense fibrillary plaques along with neurofibrils.

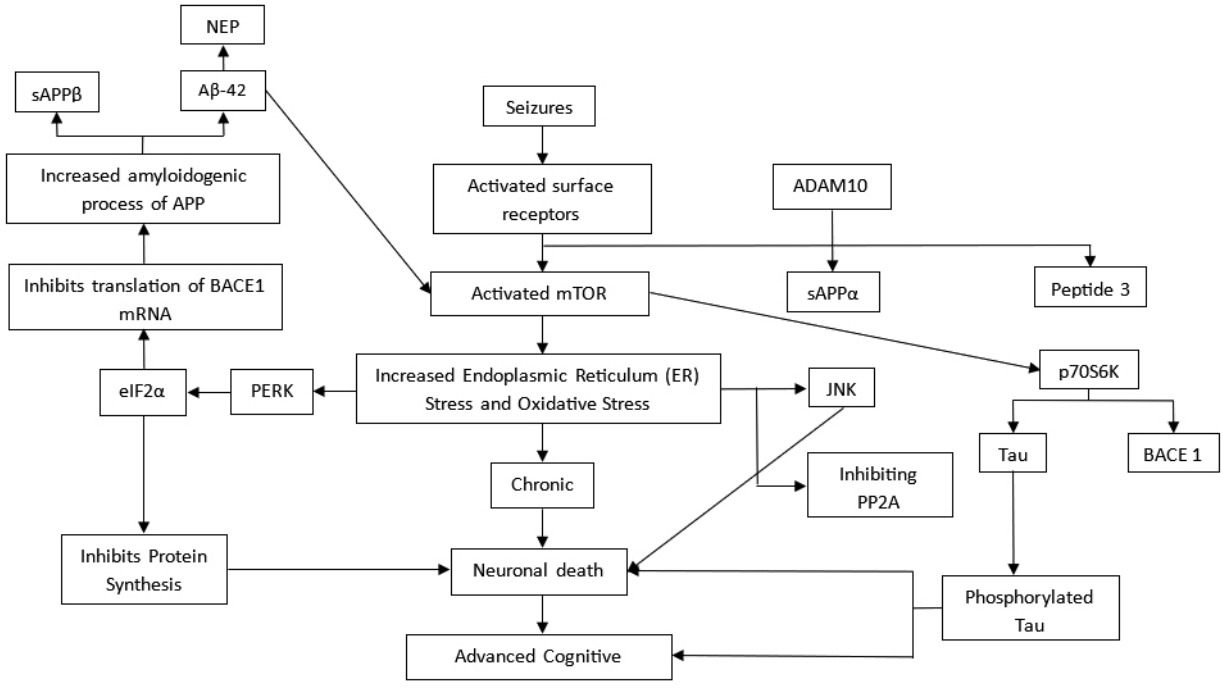

Figure 1. Role of tau and beta-amyloid in neuronal death
JNK: Jun N-terminal kinase, PERK: Pancreatic eIF2 kinase-like ER kinase, BACE1: Beta-site amyloid precursor protein (APP) cleaving enzyme 1

These neurofibrils consist of phosphorylated tau protein deposits in the cytoplasm. This is a typical histopathological finding of AD. The buildup of neuritic plaques and NFT can have toxic effects on neurons, causing dendrite shrinkage, synapse changes, and ultimately neuronal death.[24] Research using post-mortem analysis has shown that Aβ pathology spreads from the basal-frontal and temporal lobes to the hippocampus, limbic system, and finally to the entire neocortex. Aβ accumulation increases and amplifies the burden of tau pathology, triggering its spread beyond the temporal lobe and leading to neurodegeneration manifested as Aβ-facilitated tauopathy. The relationship between Aβ and epilepsy has also been investigated in clinical studies in patients with refractory epilepsy (RE) who underwent resection of the temporal lobe or part of the hippocampus. The study results showed increased expression of the Aβ precursor protein (β-APP) in patients with RE compared to the control group. Immunostaining also confirmed the localization of β-APP mainly in the neuronal cytoplasm and axons of patients with RE. These findings indicate that increased expression of β-APP may play an important role in the pathological mechanisms underlying RE.[25] In patients with TLE who are drug unresponsive, and undergo temporal lobe resection, several molecular changes resemble those seen in patients with AD, including upregulation of APP expression and increased amyloidogenic processing of APP as indicated by increased expression of phosphorylated APP, Aβ42, and Aβ56 in the hippocampus and temporal lobe cortex. Accumulation of Aβ42 can lead to cognitive dysfunction and abnormal tissue synchronization, resulting in epilepsy.[15]

Inhibition of Phosphorylated Tau and Beta-amyloid as a Novel Therapeutic Strategy in Epilepsy

Martin and Leeman-Markowski[26] showed that to prevent cells from undergoing apoptosis and restore cellular homeostasis, it is necessary to decrease caspase activity and pathways involving adenosine triphosphate (ATP), and increase tumor necrosis factor-alpha expression, along with the induction of tau phosphorylation and activation of the ER stress-induced PERK pathway. The decrease in the activity of caspase, which is an apoptotic effector protein, reduces the likelihood of further neurotoxic depolarization and cell death while promoting the restoration of cellular homeostasis. Induction of tau phosphorylation through caspase-6 cleavage indirectly reduces apoptotic signaling while maintaining cellular integrity and activates microglia, which are responsible for the degradation of tau into non-toxic components. Both caspase-3 and caspase-6 cleave tau at various sites, increasing its susceptibility to phosphorylation. However, increased tau phosphorylation reduces caspase-3 activation via a negative feedback loop. Unbalanced ER stress responses may induce atypical tau phosphorylation but have minimal acute effects. Tau oligomers (o-tau) and their aggregates activate microglia to phagocytose tau and convert it into nontoxic components. The ER stress response also upregulates Ca^{2+}-ATPases in microglia, thereby increasing the phagocytic capacity and the breakdown of tau. Tau clearance is essential for restoring cellular homeostasis and rebalancing the ER stress response after shock or injury. In addition, there is a neuroprotective response involving Aβ to restore cells to programmed apoptotic signaling and rebalance signaling dynamics between apoptosis and necrosis. In response to recurrent ER stress and unbalanced signaling dynamics between apoptosis-necrosis and atypical tau phosphorylation, Aβ activation induces ER stress responses and increases caspase-3 cleavage of Aβ precursor proteins. Nonetheless, Aβ also recruits microglia and reactive astrocytes in response to excitotoxic signals and increased tau concentration. The breakdown by microglia and reactive astrocytes of toxic tau and Aβ aggregates, reduces the effects of seeding and spreading of tau associated with Aβ. However, as increased microglial activity is indirectly induced by the presence of Aβ, this mechanism also has detrimental effects because it is linked to apolipoprotein E, amyloidosis, microglial transcriptional pathways, and ongoing neuroinflammation. Along with inflammation and microglial activation, reactive astrocytes are upregulated and recruited to clear toxic tau and Aβ, and subsequently drive cells towards apoptotic signaling. Ultimately, the reduction of inflammatory signals, as well as the phosphorylation of tau and beta-amyloid, are required once the signaling dynamics between apoptosis and necrosis are balanced to prevent the transition to irreversible degenerative pathways.[26] Owing to its negative impact leading to apoptosis, Aβ involvement is referred to as the final step in neuroprotection.

Emerging research indicates that AD and epilepsy share common neuropathological characteristics. Both conditions exhibit significantly reduced levels of Aβ42 in comparison to healthy age-matched controls. This reduction in cerebrospinal fluid Aβ42 is believed to result from the aggregation of Aβ42 into amyloid plaques within the brain. Aducanumab and lecanemab are anti-amyloid antibodies that have received United States Food and Drug Administration (FDA) approval for the treatment of AD.[27] Anti-amyloid monoclonal antibodies, which significantly reduce Aβ plaques, are linked to an adverse event known as amyloid-related imaging abnormalities (ARIA). This can manifest with oedema (ARIA-E), microhaemorrhages, or superficial siderosis (ARIA-H). Meta-analyses of clinical trials involving 9.429 patients treated with anti-Aβ immunotherapy reported overall incidences of ARIA-E and ARIA-H at 6.5% and 7.8%, respectively, with 80.4% of ARIA cases being asymptomatic.[28] ARIA is thought to result from a temporary increase in vascular permeability caused by enhanced trafficking of parenchymal Aβ to the perivascular space and/or blood vessel leakage following vascular Aβ clearance. However, with continued antibody-mediated amyloid clearance, the structural integrity of the vessels may recover, and the incidence of ARIA typically declines after 6 to 9 months of treatment.[29]

Alongside amyloid pathology, tau deposition also plays a role in the link between neurodegenerative disorders and epilepsy.[26] Tau-centric treatments can be an option for treating epilepsy. Suvorexant, an FDA-approved medication for insomnia, has been shown to reduce tau phosphorylation at specific sites and lower Aβ concentrations compared to a placebo. A 20 mg dose of suvorexant decreases tau phosphorylation and Aβ levels over time, demonstrating its efficacy. Suvorexant 20 mg, Approved by the FDA for treating insomnia, including in patients with mild-to-moderate AD, has a strong safety record. However, the 10 mg dose does not exhibit the same effects on Aβ or phosphorylated tau as the 20 mg dose.[30] Moreover, clinical studies suggest that, in hypertensive epilepsy patients, inhibiting the renin-angiotensin-aldosterone system may decrease epilepsy incidence over time. While these findings do not establish a causal relationship, they highlight the potential role of anti-hypertensive drugs, particularly angiotensin 2 receptor blockers, in preventing hypertension-related secondary complications like epilepsy. This approach could represent a novel therapeutic avenue for epilepsy through renin-angiotensin-aldosterone system inhibition.[31] The development

of numerous innovative antiseizure medications with diverse mechanisms of action has significantly broadened the range of available therapeutic options. Anti-amyloid antibodies represent a promising approach; however, their use is accompanied by potential benefits and side effects, resulting in both advantages and disadvantages. Additionally, anti-tau antibodies hold theoretical potential as an option in epilepsy therapy.

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Authorship Contributions

Concept: J.K., B.A.M., Design: J.K., B.A.M., Data Collection or Processing: B.A.M., Analysis or Interpretation: B.A.M., Literature Search: B.A.M., Writing: J.K., B.A.M.

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