ABSTRACT

The neural mechanisms of Alzheimer's Disease and Acquired Epilepsy: An investigation to understand whether an overlap exist between these two disorders

Pranav Sreekumar

Director: Joaquin Lugo, Ph.D.

Alzheimer's Disease and acquired epilepsy are neurodegenerative diseases that cause a major decrease in the quality-of-life. Identifying neurobiological pathways relevant to the development and progression of disease is very important. An increased amount of literature has shown involvement of neurodegenerative mechanisms in the pathophysiology of acquired epilepsies and Alzheimer's. In this review, we will identify whether an overlap of neural mechanisms exist in Alzheimer's Disease and acquired epilepsy. By understanding whether these diseases share neurobiological commonalities, future studies can potentially identify therapeutic targets to slow down disease progression and reduce cognitive symptoms of both disorders.

APPROVED BY DIRECTOR OF HONORS THESIS:

_____

Dr. Joaquin Lugo, Department of Psychology and Neuroscience

APPROVED BY THE HONORS PORGRAM:

_____

Dr. Elizabeth Corey, Director

DATE: _____

THE NEURAL MECHANISMS OF ALZHEIMER'S DISEASE AND ACQUIRED EPILEPSY: AN INVESTIGATION TO UNDERSTAND WHETHER AN OVERLAP EXIST BETWEEN THESE TWO DISORDERS

A Thesis Submitted to the Faculty of

Baylor University

In Partial Fulfillment of the Requirements for the

Honors Program

By

Pranav Sreekumar

Waco, Texas

May 2022

TABLE OF CONTENTS

CHAPTER ONE

Introduction

Alzheimer's Disease (AD) is a disorder that is known to most of society. Many individuals have witnessed this disease through a loved one or from a member in their community. Currently, there is no effective treatment that can alter the disease process or delay the disease onset. As a result, scientists constantly research this neurodegenerative disorder to find therapeutics that can alleviate symptoms and slow down the progression of this disease. AD is a common form of dementia and is characterized clinically by a progressive decline in cognitive function. Deficits in memory and other cognitive functions in the early stage of AD development occur due to alterations in the hippocampus and entorhinal cortex (Kocahan and Dogan 2017). The hippocampus is a structure that lies under the medial temporal lobe in the brain and has functions in learning and memory. It is connected to the entorhinal cortex, which provides the main source of input to the hippocampus. The connections that exist between these two structures occur via the dentate gyrus, which is adjacent to the hippocampus (Li et al., 2009). Behavioral studies have demonstrated that these structures play critical roles in learning and memory through the process of long-term potentiation and synaptic remodeling (Bliss & Lomo 1973). Damage to these brain structures occur in the early stages of Alzheimer's Disease and result in mild cognitive impairment (Mu and Gage 2011). As many as 80% of the neurons in the hippocampus may die over the course of the disease progression of this disorder (Morris and Kopelman 1986). Most people diagnosed with this disease are typically older with the average age being 65+ years old (Blennow et

al., 2006). However, early-onset of AD can occur in a few patients and is characterized by significant neuron loss and formation of beta-amyloid peptides and neurofibrillary tangles (Murphy and Levine 2010). Moreover, neurodegeneration in other facets of the brain include changes in neurotransmitter expression, reduced neutrophil numbers, synaptotoxicity, and accumulation of amyloid plaque deposits (Kocahan and Dogan 2017). Unfortunately, there has been no consistent treatment that modifies the disease process or slows down disease onset (Kang 2021). Despite evidence that show neurofibrillary tangles acting as biomarkers in AD, the exact role that these proteins play in the pathology of this disorder is still being investigated.

Epilepsy is widely known as one of the most common and debilitating neurologic disorders. This neurologic condition occurs in about 1% of the population and is the result of recurrent, unprovoked seizures (Stafstrom & Carmant 2015). An epileptic seizure is a transient abnormal synchronization of neurons in the brain that disrupts neurologic function due to excessive discharge of neurons (Ono and Galanopoulou 2012). Seizures can come from nonepileptic or epileptic events. The cause of an epileptic seizure is derived from many different sources that result in neural dysfunction (Shorvon 2011).

The epileptic seizure typically results from the imbalance between excitation and inhibition signals in the brain (Stafstrom and Carmant 2015). These imbalances come from a variety of changes in the neural circuits within the brain. Some seizures also come from abnormal genes and subcellular signaling cascades. The factors that result in the altered excitatory and inhibitory balance can come from either genetic or acquired causes (Stafstrom and Carmant 2015). Genetic causes result in molecular changes at the receptor level. Moreover, these genetic changes can also result in abnormal ionic channel function

(Stafstrom and Carmant 2015). Acquired epilepsy comes from different origins. Cerebral insults that result from external causes can alter the neural circuits within the brain (Stafstrom and Carmant 2015). The developing brain is more prone to seizures as the neural networks are still forming. Moreover, excitatory synaptic function develops before inhibitory synaptic function, which favors the condition of neuronal excitation and seizure generation (Stafstrom and Carmant 2015). This might explain why young individuals are more susceptible to seizures in contrast to the adult brain (Holmes and Ben-Ari 1998).

Epilepsy syndromes are usually the result of seizures that arise from a focal brain region (Stafstrom and Carmant 2015). These syndromes indicate multiple signs and symptoms that signify a unique epilepsy condition (Engel 2010). The seizures in these cases typically begin focally, but then generalize. The EEG will show focal spikes in relation to the brain area involved. Many clinicians have found that epileptic seizures originate in the temporal lobe. The neural mechanisms that result in this condition are still being investigated. A common cause of seizure genesis is impaired GABAergic inhibition, enhanced synaptic excitation, and changes in the ion channel distribution (Stafstrom and Carmant 2015). More neuroimaging data needs to be collected to better understand the specific neural mechanism that result in the development of epilepsy syndrome.

Acquired epilepsy is a subtype of epilepsy that differs from genetic epilepsy in how the disease develops. This disorder results from a variety of causes ranging from stroke to traumatic brain injury (TBI) (Berg et al., 2010). Moreover, acquired epilepsy seems to develop as a comorbid condition with neurodegenerative diseases. As a result,

many studies are investigating the neurobiological pathways that new pharmacological therapies can target, which has shown anti-epileptogenic and disease reducing effect. By understanding the neural mechanisms of acquired epilepsy, future studies can look at the overlap of this type of epilepsy and other comorbid conditions like Alzheimer Disease, which could have therapeutic benefits on slowing disease progression of both disorders.

Alzheimer's Disease (AD) and acquired epilepsy are neurodegenerative disorders that have impacted millions of people's lives around the world. Understanding the pathologies involved in these diseases is very important in the field of medicine. Researchers have looked to understand the causes and symptoms of these disorders from a biochemical and molecular standpoint. Moreover, researchers and physicians have strived to develop therapeutics to combat disease progression and reduce symptoms. However, few articles have delved deeply to identify whether these disorders share a common neural mechanism. This literature review will look to understand the neural mechanisms involved in AD and acquired epilepsy and identify whether an overlap of mechanisms exist between the two disorders. By identifying whether an overlap exists between these diseases, researchers can investigate future therapeutics that target both pathways.

CHAPTER TWO

Description of Alzheimer Disease

Location of AD

Alzheimer Disease is primarily located in the hippocampal and entorhinal regions. The hippocampus plays a major role in memory functions. For individuals with AD, the neurocognitive symptoms include memory loss and spatial memory learning deficits. These symptoms are associated with loss of function in the hippocampus (Perl 2010). Significant atrophy is also found in the entorhinal cortex when analyzing the neural tissue in this brain region. The entorhinal cortex has many layers of neurons that are impacted by the presence of neurofibrillary tangles, which develop over the course of AD (Walsh and Selkoe 2004). This results in neuritic plaques in many of the layers and connection between the entorhinal cortex and the hippocampus are damaged and inhibited by degeneration of neurons located in these layers.

Diagnosis of AD

For many neurologists and pathologists, the diagnosis of AD and its definite stages are based on the pathogenesis of disease presented by patients. The measures of this pathology include identifying the density of neuritic amyloid plaques and neurofibrillary tangles of tau protein in the affected brain regions (Murphy and Levine 2010). Many researchers have found it difficult to determine what specific mechanisms plays a role in the development of the disease. The identification of what stage a person with AD is at can only be identified posthumously, which means that a clinical diagnosis

of AD is conjecture based off the symptoms and MRI scans of a patient (Murphy and Levine 2010). The lack of a diagnostic test for a person with AD hinders the efforts of many researchers to identify disease mechanisms. This means therapeutics and other drugs cannot be administered until a certain stage of a patient's disease development.

AD Neural Mechanism Theories

AD & Amyloid-Beta protein

A development that many neuroscientists and clinicians agree upon is that the amyloid-beta protein acts as a trigger for Alzheimer disease. These plaques play a role in causing the neuronal death associated with this disorder. Studies have shown that these amyloid-beta oligomers reduce the density of dendritic spines in the hippocampus. Atrophy within the hippocampus and the entorhinal cortex due to amyloid-beta plaque may demonstrate concrete AD progression (Murphy and Levine 2010). Furthermore, the protein misfolding of these structures are transformed into polymorphic structures, which can be correlated with the clinical progression of AD (Murphy and Levine 2010). Many researchers are studying whether amyloid-beta protein can be used as biomarkers to identify AD progression (Murphy and Levine 2010). Researchers have demonstrated that amyloid-beta protein has a significant impact on neuronal function. Another type of mechanism that plays a role in the pathogenesis of AD is the excitatory effect of neurotransmitters and its receptors, specifically in relation to glutamate.

AD & NMDA Receptors

The glutamate neurotransmitter is the excitatory neurotransmitter of the central nervous system. This molecule has many functions including neuronal plasticity, neural

transmission, memory processes, and learning (Kochan and Akillioglu 2013). Studies have shown that the pathogenesis of AD is strongly associated with alterations in glutamate signaling. Moreover, tissues affected by this disease contain high levels of glutamatergic neurons (Danysz and Parsons 2012). The term, excitotoxicity, typically occurs when glutamatergic receptors, known as NMDA receptors, are constantly activated. NMDA receptors mediate synaptic plasticity through long-term potentiation (LTP). LTP is a critical process for memory and learning functions. When these receptors undergo prolonged activation, neurodegeneration occurs as AD progresses. This occurs as Ca^{2+} elevation suppresses synaptic function, which results in greater synaptotoxicity and eventually atrophy in the hippocampal tissue. This outcome has been correlated with loss of learning and memory function in AD (Parsons et al., 1998). Researchers demonstrated further evidence of this mechanism when finding that an NMDA receptor antagonist can slow AD progression (Parsons et al., 1998).

AD & Tau

The observation of tau hyperphosphorylation has been implicated in many neurodegenerative disorders (Schneider and Mandelkow 2008). However, there is a high rate of association of neurofibrillary tangles (NFT) found in Alzheimer Disease patients. NFT develop from intracellular filamentous aggregates of hyper-phosphorylated tau protein (Schneider and Mandelkow 2008). Tau can develop into various shapes of strands, known as straight filaments or paired helical filaments (PHFs) (Schneider and Mandelkow 2008). These tau aggregates can impact other neurological structures including glial cells and astrocytes. For tau proteins polymerized into NFTs, these substances are inert and cause tau to not bind to tubulin protein, which promotes the

stability of microtubules (Iqbal et al., 2009). Instead, hyperphosphorylated tau protein is present in the cytoplasm and inhibits the assembly of microtubules. This disrupts the normal function of microtubules being used as a pathway for vesicles to transport substances along this structure (Iqbal et al., 2009). Moreover, toxic tau protein sequesters normal tau protein that is used in the formation of microtubules. When the abnormal tau protein becomes dephosphorylated, NFTs disaggregate, and the tau behaves normally. From these observations, the abnormal hyperphosphorylation of tau results in a variety of clinical symptoms expressed in AD patients (Iqbal et al., 2009).

Based off these findings, future research should understand how NFTs can be used to illustrate the degree of cognitive decline and neurodegeneration in AD patients. Through this method, hyperphosphorylation of tau can be used as a biomarker, and could lead to earlier detection of AD. Studies should also investigate the clinical effects of preventing the mis-splicing of mRNA, the hyperphosphorylation of tau, and the aggregation of tau protein. Through these studies, researchers can figure out whether clinical symptoms of AD are reduced through these treatments. Moreover, researchers should investigate whether certain therapeutic agents can reduce the ratio of toxic tau isoform toward normal tau protein isoforms (Schneider and Mandelkow 2008).

As more research delves into the pathology and clinical symptoms of AD, a common finding from various studies indicate that this disease is a clear risk factor for seizures and epilepsy. The risk of seizures increases 3 to 87 times compare to age-matched population with Alzheimer's (Pandis and Scarmeas 2012). Due to the connection of both diseases, more studies need to investigate the impact of epilepsy in

further AD course and severity. To do this, one needs to look at how epilepsy develops, and the neural mechanisms involved with this disorder.

CHAPTER THREE

Description of Acquired Epilepsy

Acquired epilepsy is a subtype of epilepsy that results from a variety of causes ranging from stroke to traumatic brain injury (TBI) (Berg et al., 2010). This disorder typically affects the temporal lobe and is associated with other disturbances including memory and learning disabilities. Moreover, acquired epilepsy seems to develop as a comorbid condition with neurodegenerative diseases. As a result, many studies are investigating the neurobiological pathways that new pharmacological therapies can target that have anti-epileptogenic and disease reducing effect. By understanding the neural mechanisms of acquired epilepsy, future studies can look at the overlap of this type of epilepsy and other comorbid conditions like Alzheimer Disease, which could have therapeutic benefits on slowing disease progression of both disorders.

Acquired Epilepsy Neural Mechanism Theories

Acquired Epilepsy & AMPA Receptor

AMPA receptors play a major role in the fast excitatory synaptic neurotransmission in the central nervous system (CNS). When abnormal hyperexcitable circuitry occurs during a seizure, excessive calcium uptake can initiate neurodegenerative processes and cause neuronal cell death (Nagarkatti et al., 2009). Like NMDA receptors, the AMPA receptors have functions in synaptic plasticity and are important in the processes of long-term potentiation, learning, and memory (Selcher et al., 2012). Studies

have indicated that this neuronal excitotoxicity caused by excessive glutamate neurotransmitter plays a role in the neurodegenerative processes of Alzheimer's dementia (Lau and Tymianski 2010). Excessive glutamate neurotransmitter is also an initial neural mechanism in acquired epilepsy and leads to increased seizures due to hyperexcitability of neurons. These processes seem to happen in the hippocampus and lead to neuronal death of interneurons that are critical to the balance of excitatory and inhibitory neurons in this region (Cavazos and Cross 2006). More studies need to look at strategies to inhibit AMPA receptor activity as this can reduce excessive excitatory responses. Moreover, intracellular calcium concentration levels induced by constant AMPA receptor activation would decrease, which could slow neurodegenerative changes that result from excitotoxic effects.

Acquired Epilepsy and Tau

Tau is a microtubule-associated protein that has many physiological functions in neurons. It plays a huge role in maintaining stabilization of microtubules and contributes to axonal transport (Casillas-Espinosa et al., 2020). This protein has been linked to many neurodegenerative diseases like AD and recent studies have linked this protein to the disease progression of acquired epilepsy (Liu et al., 2016). Hyperphosphorylated tau can aggregate and lead to the impairment of neuronal cells and neurodegeneration. These aggregates have been found in various brain samples of patients with acquired epilepsy, especially after a cerebral insult caused by traumatic brain injury (TBI). Moreover, this molecular process has led to similar neurological symptoms and cognitive decline in other neurodegenerative disorders (Shultz et al., 2015). A big indicator that

hyperphosphorylated tau plays a major role in the disease formation of epilepsy is elevated levels of this protein in cerebrospinal fluid (CSF). Elevated levels of tau in the CSF indicate both axonal and neuronal damage (Monti et al., 2015). Moreover, these patients have high rates of seizures and a greater risk to develop epilepsy (Monti et al., 2015). Abnormal aggregation of tau protein has also been implicated in excitation/inhibition balance, which result in increased seizures in patients with epilepsy or other neurological diseases (Roberson et al., 2007). This is caused by increased activity of protein phosphatase 2A (PP2A) and decreased activity of various kinase enzymes like cyclin-dependent kinase 5 (CDK5) following a traumatic brain injury (Shultz et al., 2015). More research studies should look at targeting tau pathologies as a disease-modifying treatment and a possible biomarker in predicting post-traumatic epilepsy after a cerebral insult.

Acquired epilepsy and amyloid-beta pathway

Amyloid-beta protein can be found in aggregates in various regions in the brain. These aggregates produce insoluble fibrils and plaques. These plaques have been widely documented in individuals with Alzheimer's Disease. Patients with AD who have these plaques have an increased risk of developing spontaneous seizures in comparison to the general population (Hauser et al., 1986). As a result, more studies are investigating the role amyloid-beta protein has on the pathogenesis of epilepsy, especially after an injury that causes a cerebral insult. Studies have found that epileptogenic brain injury from causes like TBI can trigger overexpression of amyloid precursor protein (APP), which is a precursor of amyloid-beta protein (Blennow et al., 2012). Studies have demonstrated

that increased amyloid production can contribute to the development of acquired epilepsy (Kenney et al., 2018). These deposits have been found in the cortex regions and the hippocampus. Amyloid-beta deposits show increased neuronal excitability and cause hyperactivation processes like epileptogenesis (Vossel et al., 2017). Hippocampal hyperactivation can cause seizures and increased epileptiform activity throughout the development of acquired epilepsy (Vossel et al., 2013). Plaques formed from amyloid-beta protein have been related to the excessive release of dopamine and dopamine receptors, which disrupts the GABAergic inhibitory input. This leads to an excitatory/inhibitory imbalance and hyperexcitability of pyramidal cells in the hippocampus (Ren et al., 2018). Moreover, amyloid-beta accumulation can cause microglia activation, which quickens the development of seizures and epilepsy (Ali et al., 2018). By understanding the neural mechanisms involved with amyloid-beta protein, researchers can develop new therapeutic targets to slow down the neurodegeneration resulting from TBIs.

CHAPTER FOUR

Relationship of AD and acquired epilepsy

As researchers learn more about the neural pathways involved in AD and epilepsy, there has been growing evidence that these 2 diseases might share common etiological mechanisms. These etiologies stem from instances of traumatic brain injury, stroke, and other forms of cerebral insults. Each of these causes have been found to promote progressive neurodegeneration for both acquired epilepsy and AD. Moreover, studies have found that acquired epilepsy commonly develops as a comorbid disease with patients who have Alzheimer's or other neurodegenerative diseases (Casillasa-Espinosa et al., 2020). These findings seem to demonstrate that acquired epilepsy can be considered a progressive disorder due to similar neural mechanisms displayed in both diseases. Studies have shown an association with various neurodegenerative pathways such as tau protein and amyloid-beta protein (Ali et al., 2019). Development of acquired epilepsy has also been associated with cognitive decline and neuropsychiatric comorbidities. Since Alzheimer's disease has a similar disease progression, these findings indicate that both disorders might share neurobiological pathways. By understanding these pathways, scientists can investigate new pharmacological therapies that has the potential to reduce the disease onset of epileptogenesis and seizure symptoms. In fact, studies using targeted therapeutics on neurodegenerative mechanisms have reported protective effects against epileptogenesis when an acquired brain insult occurs (Liu et al., 2016). These therapies could slow down the disease progression and reduce

neurocognitive symptoms associated with neurodegenerative disorders like Alzheimer's Disease. As more of these findings develop and are translated from animal models into human clinical trials, therapeutics that aim to reduce disease progression of acquired epilepsy might subsequently slow disease onset of other neurodegenerative diseases with similar mechanisms like Alzheimer's.

CHAPTER FIVE

Role of Tau Hyperphosphorylation in AD and Epilepsy

Understanding the neural mechanisms involved in Alzheimer Disease and epilepsy is a complicated endeavor that will take researchers time to disentangle. Different neural mechanisms for each neurodegenerative disorder have been studied for many years. However, there seems to be a common molecular finding related to the development of clinical symptoms for both diseases. This revolves around the abnormal phosphorylation of the tau protein (Kang 2021). This process seems to result in neurofibrillary tangles forming in the brain, which is a common pathological feature in many Alzheimer Disease patients. Moreover, tau hyperphosphorylation is observed in traumatic brain injury (TBI) patients, which is an established risk factor for epilepsy (Liu et al., 2020).

Tau is a neural-specific and microtubule-associated protein that can be phosphorylated by many kinases (Kang 2021). This protein is highly hydrophilic, which allows it to be highly soluble and heat stable (Iqbal et al., 2009). The major biological function of this protein revolves around the stabilization of microtubules in the cell (Kang 2021). The importance of microtubules revolves around the ability to grow and shrink to support cellular shape changes (Schneider and Mandelkow 2008). For neurons, microtubules also serve as the pathways for substances that are transported from vesicles along axons and dendrites (Schneider and Mandelkow 2008). Microtubules are regulated by microtubule-associated protein (MAP), which involves the tau protein. The tau protein

itself is regulated by post-translational modifications, such as phosphorylation and de-phosphorylation (Schneider and Mandelkow 2008). Tau protein is an abundant substance in neurons but found in low amounts in the central nervous system (CNS) (Kang 2021). In mature neurons, tau protein is found in the axon (Schneider and Mandelkow 2008). From a molecular viewpoint, tau is coded by a single gene on chromosome 17 but can be expressed in several isoforms due to alternative splicing of its mRNA (Iqbal et al., 2009). Tau interacts with tubulin and helps in the assembly of microtubules. In a healthy brain, tau contains 2-3 phosphates per mole of the protein, which appears to be the optimal amount for promotion of microtubule assembly (Iqbal et al., 2009).

Tau hyperphosphorylation has been see in many patients with TBI, a known established risk factor for epilepsy. However, few studies have investigated the connection between the tau protein and its similarities in the neural mechanisms of both Alzheimer's Disease and epilepsy. To better understand this relationship, studies have used mouse models to investigate the causes of genetic epilepsy from a molecular viewpoint. These studies have found that the deletion of a tau gene can reduce neuronal network hyperexcitability in mouse models of AD (Holth et al., 2013). This interaction between tau and neuronal excitability in mice with AD demonstrates that the tau protein may play a role in the development of epileptic symptoms Although there is not a clear explanation for why tau can modulate neuronal excitability, these studies demonstrate that tau removal can play a role in the reduction of neuronal network firing (Holth et al., 2013). This would result in less epileptic symptoms and reduced AD symptoms caused by the hyperphosphorylation of tau. In other studies, researchers demonstrated that protein misfolding can lead to the development of AD. Scientists have shown that

endoplasmic reticulum (ER) stress can lead to accumulation of protein misfolding, which results in excitability/inhibitory neuronal firing imbalances (Shao et al., 2015). Endoplasmic reticulum stress results in impaired memory and reduced synaptic plasticity (Lin et al., 2018). More research is needed to better understand the molecular nature of endoplasmic reticulum stress and how it results in the development of tau hyperphosphorylation, which causes cognitive impairment to develop. Some ways scientists are better understanding this process is developing treatments to relieve endoplasmic reticulum stress. Future studies should investigate the benefits of relieving endoplasmic reticulum stress and how limiting tau hyperphosphorylation can improve memory and reduce excitatory/inhibitory neuronal imbalance.

Recent studies have shown that neuronal network hyperexcitability underlies the pathogenesis of epileptic seizures (Holth et al., 2013). This phenomenon also seems to be a component of various neurodegenerative disorders like Alzheimer's disease. A common biomolecular finding in both diseases is the existence of the protein tau. The microtubule-binding tau has been shown to regulate the neuronal excitability levels in people with epilepsy (Holth et al., 2013). Mouse studies have demonstrated that removal of the Map gene encoding tau results in decreased hyperexcitability and a stabilization of excitation/inhibition levels (Holth et al., 2013). Moreover, this removal of the tau protein gene reduces cognitive dysfunction/symptoms in individuals with Alzheimer Disease (Holth et al., 2013). The tau protein can also result in axonal transport deficits and changes in synaptic long-term potentiation, which can result in epileptogenesis (Holth et al., 2013). Researchers have found that the expression of the ApoE4 gene, which is an AD risk factor allele, plays a role in neuronal network hyperexcitability (Hunter et al.,

2012). A study done by Holth et al., 2013, looked to further understand whether removal of tau can result in suppression of epilepsy in AD mouse models. These researchers found that tau loss plays a major role in limiting cortical network excitability, even in the absence of AD-molecular pathology. Moreover, reduction of tau protein could improve cognition in AD mouse models to go along with the reduction of hyperexcitability found. This demonstrates that tau protein has a huge impact in the pathogenesis of Alzheimer Disease and epilepsy. Future studies could investigate the pharmacological benefits of tau dephosphorylation and tau protein reduction. The effects of these molecular changes show reduction of hyperexcitability in neuronal networks, which is a common feature in many patients with epilepsy. Moreover, these treatments could reduce the cognitive symptoms that result in individuals with early-onset AD.

CHAPTER SIX

Role of Glutamate Receptors in Both AD and Epilepsy

Another neural mechanism that might overlap between Alzheimer's Disease and acquired epilepsy is the role that glutamate receptors play in both diseases. Glutamate neurotransmitters are known to take an excitatory role in the central nervous system. This molecule is a key contributor to many functions including memory processes and neuronal plasticity (Kochan and Akillioglu, 2013). The key receptors in these processes are the NMDA and AMPA receptors. Similar excitotoxicity functions of these receptors have been found in both diseases. In Alzheimer's disease, pathogenesis of AD has been associated with high levels of glutamatergic neurons that constantly activate NMDA receptors. During the pathogenesis of acquired epilepsy, AMPA receptors play a role in the fast excitatory synaptic neurotransmission that results in abnormal hyperexcitable circuitry. Both neural mechanisms occur in the hippocampus and can lead to imbalance of excitatory and inhibitory neurons (Cavazos and Cross 2006). This illustrates that acquired epilepsy and AD could have similar effects due to constant activation of AMPA and NMDA receptors.

Recent studies have found that epileptogenesis can develop from the transformation of healthy brain tissue into hyperexcitable neuronal networks (Nagarkatti et al., 2009). This process demonstrates that constant activation of AMPA receptor can lead to increased intracellular calcium levels during seizures. Hyperexcitable neuronal networks have also been found in the disease progression of Alzheimer's Disease.

Similar to epileptogenesis, constant glutamate receptor activation results in heightened intracellular calcium levels. Elevated calcium levels can suppress synaptic function and result in greater synaptotoxicity and atrophy of hippocampal tissue, which is correlated with loss of learning and memory function in AD (Parsons et al., 1998).

These findings demonstrate that glutamate receptors can impact the pathogenesis of acquired epilepsy and Alzheimer's Disease. More studies should investigate targeted therapies in the hippocampus that aim to reduce intracellular calcium levels that result from constant activation of NMDA and AMPA receptors. By reducing calcium levels, this could slow disease progression and limit the symptoms of both disorders including memory loss and seizures.

CHAPTER SEVEN

Discussion

Based off the literature, there are significant neuropathological and neurobiological parallels between Alzheimer's disease and acquired epileptogenesis. The protein tau plays a major role in the disease progression of both disorders. Specifically, hyperphosphorylation of tau has been shown to cause neuronal excitability in patients and mice models for both diseases. Hyperphosphorylation of tau results in protein misfolding and increased amounts of neurofibrillary tangles, which is a characteristic in patients with Alzheimer's disease. This leads to excitatory/inhibitory neuronal firing imbalance. Similar findings are found in patients with acquired epilepsy. Tau is a protein found to regulate the neuronal excitability levels in patients with epilepsy (Holth et al., 2013). Using mouse models, researchers demonstrated that removal of the Map gene encoding tau results in decreased hyperexcitability and a stabilization of excitation/inhibition levels (Holth et al., 2013). Moreover, this removal of the tau protein gene reduces cognitive dysfunction/symptoms in individuals with Alzheimer Disease (Holth et al., 2013). These findings indicate that lowering the amount of tau protein can play a role in slowing down disease progression and reduce neuronal network excitability found in the hippocampus region.

Alzheimer's disease and acquired epilepsy have another similar neural mechanism with the role that glutamate receptors play in both diseases. Glutamate is a key neurotransmitter that functions in memory processes and neuronal plasticity. When an excess amount of this molecule binds to the NMDA and AMPA glutamate receptors,

excitotoxic functions have been found in both disorders. There seems to be increased levels of intracellular calcium ions that enter the cell, which causes greater synaptic dysfunction and atrophy of hippocampal tissue. These findings are correlated with loss of learning and memory function in AD (Parsons et al., 1998). With these results, researchers should investigate targeted therapeutics aimed at the hippocampus that look to reduce intracellular calcium levels. By reducing constant activation of glutamate receptors, this could potentially limit disease progression for both disorders.

From these findings, the literature demonstrates that an overlap of neural mechanisms exists between Alzheimer's Disease and acquired epilepsy. Understanding the neurobiology of both disorders has shown commonalities in the misfolding of tau and hyperactivation of glutamate receptors. More research needs to be conducted on mouse models to further understand the connection between AD and acquired epilepsy. Further solidification of these neurobiological pathways will allow scientists to investigate targeted therapeutics that could reduce the severity of cognitive symptoms and slow down disease-onset in both diseases.

CHAPTER EIGHT

Conclusion

The pathophysiology of AD and acquired epilepsy are complex processes made up from various neural mechanisms. Despite separate disease progressions, researchers indicate a connection exists between the neural mechanisms involved in both disorders. To better understand this relationship, researchers need to study more cases of AD patients who are prone to develop epileptic seizures. Moreover, studies need to translate the findings found in mouse models and see whether these results exist in human patients. Understanding whether an overlap of neural mechanisms exist would allow researchers to acquire insight on therapeutics that can slow down disease progression and reduce the severity of symptoms in both diseases. Before scientists get to this point, future studies need to test targeted therapeutics on these mechanisms using animal models and see whether clinical symptoms are reduced for both disorders. Once researchers demonstrate that a consistent therapeutic effect exists from these studies, then testing on Alzheimer's Disease and acquired epilepsy patients can start.

GLOSSARY

Hippocampus: Region in the brain that plays a fundamental role in some forms of learning and memory. Part of a functional brain system called the hippocampal formation, which includes the dentate gyrus, subiculum, presubiculum, parasubiculum, and entorhinal cortex.

Entorhinal Cortex: Main gateway into the hippocampus. Located near the amygdala, which is a structure in the brain known to play role in emotions and fear learning. Reciprocal connections between this cortex and the hippocampus.

Amyloid Precursor Protein (APP): Transmembrane protein that has a major role in the regulation of certain functions in the nervous system. This protein is known to promote synaptogenesis and synaptic plasticity. Comes from the amyloid precursor gene.

Microglia: Immune cells of the central nervous system and plays an important role in inflammation. These cells typically respond to pathological disturbances and have a wide range of effects when activated to confer neuronal protection. Under normal physiological conditions, these cells shape neural circuit activity and have a protective role for neurons.

NMDA Receptor: Glutamate and ion channel receptor that is activated when glutamate and glycine bind to it. This receptor is a heteromeric complex that has 3 different subunits: GluN1, GluN2, and GluN3. Controls the influx of calcium and sodium ions into the cell.

AMPA Receptor: Subtype of the ionotropic glutamate receptor. Coupled to ion channels that modulate cell excitability by controlling the flow of potassium and sodium ions into the cell.

REFERENCES

Ali, I., Silva, J. C., Liu, S., Shultz, S. R., Kwan, P., Jones, N. C., & O'Brien, T. J. (2019). Targeting neurodegeneration to prevent post-traumatic epilepsy. *Neurobiology of Disease*, *123*, 100–109. https://doi.org/10.1016/j.nbd.2018.08.006

Berg, A. T., Berkovic, S. F., Brodie, M. J., Buchhalter, J., Cross, J. H., van Emde Boas, W., Engel, J., French, J., Glauser, T. A., Mathern, G. W., Moshé, S. L., Nordli, D., Plouin, P., & Scheffer, I. E. (2010). Revised terminology and concepts for organization of seizures and epilepsies: Report of the Ilae Commission on classification and terminology, 2005-2009. *Epilepsia*, *51*(4), 676–685. https://doi.org/10.1111/j.1528-1167.2010.02522.x

Blennow, K., de Leon, M. J., & Zetterberg, H. (2006). Alzheimer's disease. *The Lancet*, *368*(9533), 387–403. https://doi.org/10.1016/s0140-6736(06)69113-7

Blennow, K., Hardy, J., & Zetterberg, H. (2012). The neuropathology and Neurobiology of Traumatic Brain Injury. *Neuron*, *76*(5), 886–899. https://doi.org/10.1016/j.neuron.2012.11.021

Bliss, T. V., & Lømo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the Perforant Path. *The Journal of Physiology*, *232*(2), 331–356. https://doi.org/10.1113/jphysiol.1973.sp010273

Casillas-Espinosa, P. M., Ali, I., & O'Brien, T. J. (2020). Neurodegenerative pathways as targets for acquired epilepsy therapy development. *Epilepsia Open*, *5*(2), 138–154. https://doi.org/10.1002/epi4.12386

Cavazos, J. E., & Cross, D. J. (2006). The role of synaptic reorganization in Mesial Temporal Lobe epilepsy. *Epilepsy & Behavior*, *8*(3), 483–493. https://doi.org/10.1016/j.yebeh.2006.01.011

Danysz, W., & Parsons, C. G. (2012). Alzheimer's disease, β-amyloid, glutamate, NMDA receptors and memantine - searching for the connections. *British Journal of Pharmacology*, *167*(2), 324–352. https://doi.org/10.1111/j.1476-5381.2012.02057.x

Engel Jr., J. (2010). Do we belittle epilepsy by calling it a disorder rather than a disease? *Epilepsia*, *51*(11), 2363–2364. https://doi.org/10.1111/j.1528-1167.2010.02701.x

Hauser, W. A., Morris, M. L., Heston, L. L., & Anderson, V. E. (1986). Seizures and myoclonus in patients with alzheimer's disease. *Neurology*, *36*(9), 1226–1226. https://doi.org/10.1212/wnl.36.9.1226

Holmes, G. L., & Ben-Ari, Y. (1998). Seizures in the developing brain. *Neuron*, *21*(6), 1231–1234. https://doi.org/10.1016/s0896-6273(00)80642-x

Holth, J. K., Bomben, V. C., Reed, J. G., Inoue, T., Younkin, L., Younkin, S. G., Pautler, R. G., Botas, J., & Noebels, J. L. (2013). Tau loss attenuates neuronal network hyperexcitability in mouse and drosophila genetic models of epilepsy. *Journal of Neuroscience*, *33*(4), 1651–1659. https://doi.org/10.1523/jneurosci.3191-12.2013

Iqbal, K., Liu, F., Gong, C.-X., Alonso, A. del, & Grundke-Iqbal, I. (2009). Mechanisms of tau-induced neurodegeneration. *Acta Neuropathologica*, *118*(1), 53–69. https://doi.org/10.1007/s00401-009-0486-3

Kang, J.-Q. (2021). Epileptic mechanisms shared by alzheimer's disease: Viewed via the unique lens of genetic epilepsy. *International Journal of Molecular Sciences*, *22*(13), 7133. https://doi.org/10.3390/ijms22137133

Kenney, K., Iacono, D., Edlow, B. L., Katz, D. I., Diaz-Arrastia, R., Dams-O'Connor, K., Daneshvar, D. H., Stevens, A., Moreau, A. L., Tirrell, L. S., Varjabedian, A., Yendiki, A., van der Kouwe, A., Mareyam, A., McNab, J. A., Gordon, W. A., Fischl, B., McKee, A. C., & Perl, D. P. (2017). Dementia after moderate-severe traumatic brain injury: Coexistence of multiple Proteinopathies. *Journal of Neuropathology & Experimental Neurology*, *77*(1), 50–63. https://doi.org/10.1093/jnen/nlx101

Kocahan, S., & Akillioglu, K. (2013). Effects of NMDA receptor blockade during the early development period on the retest performance of adult Wistar rats in the elevated plus maze. *Neurochemical Research*, *38*(7), 1496–1500. https://doi.org/10.1007/s11064-013-1051-y

Kocahan, S., & Doğan, Z. (2017). Mechanisms of alzheimer's disease pathogenesis and prevention: The brain, neural pathology, N-methyl-D-aspartate receptors, tau protein and other risk factors. *Clinical Psychopharmacology and Neuroscience*, *15*(1), 1–8. https://doi.org/10.9758/cpn.2017.15.1.1

Lau, A., & Tymianski, M. (2010). Glutamate receptors, neurotoxicity and neurodegeneration. *Pflügers Archiv - European Journal of Physiology*, *460*(2), 525–542. https://doi.org/10.1007/s00424-010-0809-1

Li, Y., Mu, Y., & Gage, F. H. (2009). Development of neural circuits in the adult hippocampus. *Current Topics in Developmental Biology*, *87*, 149–174. https://doi.org/10.1016/s0070-2153(09)01205-8

Lin, L., Cao, J., Yang, S. S., Fu, Z. Q., Zeng, P., Chu, J., Ning, L. N., Zhang, T., Shi, Y., Tian, Q., Zhou, X. W., & Wang, J. Z. (2018). Endoplasmic reticulum stress induces spatial memory deficits by activating gsk -3. *Journal of Cellular and Molecular Medicine*, *22*(7), 3489–3502. https://doi.org/10.1111/jcmm.13626

Monti, G., Tondelli, M., Giovannini, G., Bedin, R., Nichelli, P. F., Trenti, T., Meletti, S., & Chiari, A. (2015). Cerebrospinal fluid tau proteins in status epilepticus. *Epilepsy & Behavior*, *49*, 150–154. https://doi.org/10.1016/j.yebeh.2015.04.030

Morris, R. G., & Kopelman, M. D. (1986). The memory deficits in alzheimer-type dementia: A Review. *The Quarterly Journal of Experimental Psychology Section A*, *38*(4), 575–602. https://doi.org/10.1080/14640748608401615

Mu, Y., & Gage, F. H. (2011). Adult hippocampal neurogenesis and its role in alzheimer's disease. *Molecular Neurodegeneration*, *6*(1), 85. https://doi.org/10.1186/1750-1326-6-85

Murphy, M. P., & LeVine, H. (2010). Alzheimer's disease and the amyloid-β peptide. *Journal of Alzheimer's Disease*, *19*(1), 311–323. https://doi.org/10.3233/jad-2010-1221

Nagarkatti, N., Deshpande, L. S., & DeLorenzo, R. J. (2009). Development of the Calcium Plateau following status epilepticus: Role of calcium in epileptogenesis. *Expert Review of Neurotherapeutics*, *9*(6), 813–824. https://doi.org/10.1586/ern.09.21

Ono, T., & Galanopoulou, A. S. (2012). Epilepsy and epileptic syndrome. *Advances in Experimental Medicine and Biology*, *724*, 99–113. https://doi.org/10.1007/978-1-4614-0653-2_8

Palop, J. J., & Mucke, L. (2010). Amyloid-β–induced neuronal dysfunction in Alzheimer's disease: From synapses toward Neural Networks. *Nature Neuroscience*, *13*(7), 812–818. https://doi.org/10.1038/nn.2583

Pandis, D., & Scarmeas, N. (2012). Seizures in alzheimer disease: Clinical and Epidemiological Data. *Epilepsy Currents*, *12*(5), 184–187. https://doi.org/10.5698/1535-7511-12.5.184

Parsons, C. G., Danysz, W., & Quack, G. (1998). Glutamate in CNS disorders as a target for drug development: An update. *Drug News & Perspectives*, *11*(9), 523–569. https://doi.org/10.1358/dnp.1998.11.9.863689

Perl, D. P. (2010). Neuropathology of Alzheimer's disease. *Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine*, *77*(1), 32–42. https://doi.org/10.1002/msj.20157

Ren, S.-Q., Yao, W., Yan, J.-Z., Jin, C., Yin, J.-J., Yuan, J., Yu, S., & Cheng, Z. (2018). Amyloid β causes excitation/inhibition imbalance through dopamine receptor 1-dependent disruption of fast-spiking GABAergic input in anterior cingulate cortex. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-017-18729-5

Roberson, E. D., Scearce-Levie, K., Palop, J. J., Yan, F., Cheng, I. H., Wu, T., Gerstein, H., Yu, G.-Q., & Mucke, L. (2007). Reducing endogenous tau ameliorates amyloid ß-induced deficits in an alzheimer's disease mouse model. *Science*, *316*(5825), 750–754. https://doi.org/10.1126/science.1141736

Schneider, A., & Mandelkow, E. (2008). Tau-based treatment strategies in neurodegenerative diseases. *Neurotherapeutics*, *5*(3), 443–457. https://doi.org/10.1016/j.nurt.2008.05.006

Selcher, J. C., Xu, W., Hanson, J. E., Malenka, R. C., & Madison, D. V. (2012). Glutamate receptor subunit GLUA1 is necessary for long-term potentiation and synapse unsilencing, but not long-term depression in mouse hippocampus. *Brain Research*, *1435*, 8–14. https://doi.org/10.1016/j.brainres.2011.11.029

Shao, Y., Li, M., Wu, M., Shi, K., Fang, B., & Wang, J. (2015, November 15). *FAD-linked presenilin-1 V97L mutation impede Tranport regulation and intracellular ca(2+) homeostasis under ER stress*. International journal of clinical and experimental medicine. Retrieved April 7, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4723842/

Shorvon, S. D. (2011). The causes of epilepsy: Changing concepts of etiology of epilepsy over the past 150 years. *Epilepsia*, *52*(6), 1033–1044. https://doi.org/10.1111/j.1528-1167.2011.03051.x

Shultz, S. R., Wright, D. K., Zheng, P., Stuchbery, R., Liu, S.-J., Sashindranath, M., Medcalf, R. L., Johnston, L. A., Hovens, C. M., Jones, N. C., & O'Brien, T. J. (2015). Sodium selenate reduces hyperphosphorylated tau and improves outcomes after traumatic brain injury. *Brain*, *138*(5), 1297–1313. https://doi.org/10.1093/brain/awv053

Stafstrom, C. E., & Carmant, L. (2015). Seizures and epilepsy: An overview for neuroscientists. *Cold Spring Harbor Perspectives in Medicine*, *5*(6). https://doi.org/10.1101/cshperspect.a022426

Vossel, K. A., Beagle, A. J., Rabinovici, G. D., Shu, H., Lee, S. E., Naasan, G., Hegde, M., Cornes, S. B., Henry, M. L., Nelson, A. B., Seeley, W. W., Geschwind, M. D., Gorno-Tempini, M. L., Shih, T., Kirsch, H. E., Garcia, P. A., Miller, B. L., & Mucke, L. (2013). Seizures and epileptiform activity in the early stages of alzheimer disease. *JAMA Neurology*, *70*(9), 1158. https://doi.org/10.1001/jamaneurol.2013.136

Vossel, K. A., Tartaglia, M. C., Nygaard, H. B., Zeman, A. Z., & Miller, B. L. (2017). Epileptic activity in alzheimer's disease: Causes and clinical relevance. *The Lancet Neurology*, *16*(4), 311–322. https://doi.org/10.1016/s1474-4422(17)30044-3

Walsh, D. M., & Selkoe, D. J. (2004). Deciphering the molecular basis of memory failure in alzheimer's disease. *Neuron*, *44*(1), 181–193. https://doi.org/10.1016/j.neuron.2004.09.010