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Disruption of Long-Term Potentiation in Alzheimer's Disease: Molecular Mechanisms and Therapeutic Solutions

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ABSTRACT

Memory mechanisms such as long-term potentiation count on synaptic plasticity, the ability of connections between neurons to strengthen or weaken through excitatory and inhibitory signals. Alzheimer's Disease (AD) is the most common cause of dementia due to its pathologies that inhibit LTP, such as amyloid-β oligomers, neurofibrillary tangles, and neuroinflammation. Studies have shown these mechanisms to damage synaptic plasticity, but the field is still very controversial regarding the approach for treatments. This paper reviews the role of LTP and LTD in normal synaptic function, how AD pathology damages this synaptic function, and the most notable treatments in the industry. The synthesized conclusion of this review is that amyloid-β, neurofibrillary tangles, and neuroinflammation are not only the main causes of deteriorated synaptic plasticity, but they can be seen as an interconnected network of pathologies that stem from each other. Understanding the true relationship among these pathologies is important for improving our understanding of AD as a whole.

INTRODUCTION

Memory is one of the critical aspects of human function. It allows humans to maintain their level of complex cognitive lives. Scientists have discovered numerous forms of memory in the brain and different mechanisms for encoding, storing, and retrieving that information. Memory can be characterized into four categories: sensory memory, short-term memory, working memory, and long-term memory (**Loprinzi, 2018)**. Alzheimer's Disease poses one of the greatest unsolved problems of our time, as it is the largest cause of dementia in humans, and despite decades of research, we possess no cure to halt the progression of this pathology or reverse the damage caused. Understanding molecular processes in Alzheimer's Disease is the only way we can get closer to curing it. This paper will go over the mechanism of LTP, how Alzheimer's affects it, and the most appealing treatments for Alzheimer's.

This review synthesizes peer-reviewed literature on synaptic plasticity dysfunction in Alzheimer's disease. Relevant studies were identified through systematic searches of PubMed and Google

Scholar. Targeted keywords related to LTP, LTD, amyloid-β, and tau protein were used. Studies with strong experimental design and relevance to therapeutic interventions were prioritized.

MECHANISMS OF LONG-TERM POTENTIATION

Long-Term Potentiation (LTP)

Long-term memory can be divided into explicit memory, the conscious recollection of facts and events, and implicit memory, unconscious memory for performing skills (**Lomo et al., 1966)**. LTP is primarily associated with explicit/declarative memory and is prominent in the hippocampus region of the brain. LTP is the strengthening of synaptic connections through increased and repeated stimulations of synapses by action potentials and was first discovered by Terje Lomø. While LTP strengthens connections, long-term depression (LTD) is the removal of synaptic connections after a lack of stimulation. LTP is divided into two distinct phases: early phase LTP (E-LTP) and late phase LTP (L-LTP).

Early Phase LTP (E-LTP)

E-LTP is characterized by its use of existing protein structures for the molecular processes and its fast, transient nature compared to L-LTP **(Bear and Malenka, 1994; Bliss and Lomo, 1973)**. E-LTP is caused by a sudden and brief high-frequency stimulation through excitatory action potentials. These action potentials lead to the release of glutamate, a neurotransmitter, from the presynaptic neuron **(Loprinzi, 2018)**. This glutamate is essential for the transmission of the excitatory action potential. The postsynaptic neuron has two protein receptors that are essential for this process: AMPAR and NMDAR. The released glutamate first attaches to an AMPA receptor on the postsynaptic neuron, which allows for the depolarization of the postsynaptic membrane through the influx of Na^+ ions. These Na^+ ions cause the Mg^{2+} block in the NMDA receptor to be removed due to electrostatic repulsion. This opens up the NMDA receptor, allowing Ca^{2+} ions to flow into the neuron. The Ca^{2+} influx is essential for the rest of E-LTP and the processes in L-LTP.

After the Ca^{2+} enters the neuron, it binds to a protein known as calmodulin, which activates calcium/calmodulin-dependent protein kinase II (CaMKII), a kinase used to phosphorylate proteins to activate them. Phosphorylation is the process of attaching a phosphate group to a protein to alter its structure or function, which influences its activity. CaMKII is an important kinase that phosphorylates AMPA receptors. Phosphorylating AMPA receptors leads to increased sensitivity to glutamate and the insertion of new AMPA receptors into the postsynaptic membranes. Through this mechanism, E-LTP can improve the strength of stimulated synapses.

Long-Term Depression (LTD)

Long-term depression (LTD) is a reduction in synaptic strength most commonly triggered by low-frequency stimulation (LFS) **(Bear and Malenka, 1994).** In their study, Bear and Malenka pointed

out that in the hippocampal CA1 region, LTD is homosynaptic and depends on NMDAR-mediated Ca^{2+} entry. This means that the process of LTD is restricted to only the activated synapses and cannot affect other synaptic connections. Unlike LTP, which requires a brief and large rise in intracellular calcium that activates protein kinases, LTD arises from a smaller and sustained Ca^{2+} elevation that activates serine/threonine protein phosphatases such as PP1 and PP2A. These enzymes dephosphorylate important phosphoproteins, including those regulating AMPAR conductivity. This leads to a reduction of the excitatory signals in the postsynaptic neuron, essentially weakening the synaptic connection. Bear and Malenka proposed that LTP and LTD functioned in the same location but in different directions: one used phosphorylation for the strengthening of synapses, and the other used dephosphorylation to weaken synaptic connections. This two-way system allows us to tune and manage our memories by pruning unnecessary synapses and growing useful synapses.

In summary, LTP and LTD work together to regulate synaptic strength, supporting the encoding and consolidation stages of memory. While E-LTP relies on quick, local changes to receptors, L-LTP involves the use of complex cascading networks of kinase signaling in order for gene transcription and structural development.

Synaptic Biology

LTP and LTD depend on several cellular components beyond the neurons themselves. These components are referenced throughout this paper in the context of AD pathology, so it is important to first understand their normal function.

Glial cells are cells in the brain that support neurons and maintain the surrounding environment **(Li et al., 2009).** Two types of glial cells are especially relevant to synaptic plasticity: astrocytes and microglia. Astrocytes are cells responsible for regulating the chemical environment of synapses. One of their most important roles is the uptake of glutamate from the synaptic cleft through transporter proteins such as GLT-1 and GLAST. This uptake maintains glutamate homeostasis, which is the proper regulation of glutamate concentrations in the extracellular space. If glutamate is not cleared effectively, the excess can overactivate receptors on the postsynaptic neuron and cause excitotoxicity and neuronal damage. Microglia are the immune cells of the brain. Under normal conditions, they survey the neural environment and clear extracellular debris through phagocytosis, the process of engulfing and eliminating unwanted material.

The maintenance of synaptic strength also depends on the proper trafficking of receptors to and from the postsynaptic membrane. One mechanism involved in this trafficking is clathrin-mediated endocytosis (CME). CME is a process in which the protein clathrin forms a vesicle around receptors on the membrane surface to internalize them into the cell. Under normal conditions, CME allows neurons to regulate the number of AMPARs at the synapse, which directly influences how strong that synaptic connection is.

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that supports neuron survival, growth, and synaptic plasticity. BDNF is synthesized through gene transcription pathways activated during L-LTP and is transported along axons by microtubules to reach synaptic sites. BDNF exerts its effects by binding to

tropomyosin receptor kinase B (TrkB), a receptor that activates downstream signaling cascades involved in the structural changes associated with long-term memory.

HOW ALZHEIMER'S DISEASE AFFECTS LTP

Alzheimer's Disease

Alzheimer's Disease (AD) was first reported by Alois Alzheimer in 1906 **(Holtzman et al., 2011; Selkoe, 2022; Heneka, 2015; Koffie et al., 2011).** His clinical study on middle-aged women experiencing strange cases of dementia found a correlation between neurofibrillary change in the cerebral cortex and the women's pathological conditions. In modern times, AD is the leading cause of dementia with no effective cure to halt its progression or reverse existing damage. AD is pathologically characterized by the accumulation of amyloid-β (Aβ) plaques in extracellular regions and neurofibrillary tangles caused by hyperphosphorylated tau protein. These molecular changes caused by AD's pathologies are responsible for widespread synapse loss and neuroinflammation driven by microglial and astrocyte dysfunction.

Amyloid-β Plaques

Amyloid-β (Aβ) is a central pathological symptom of AD **(Masters and Selkoe, 2012; Coronel et al., 2018; Palop and Mucke, 2010).** This pathology arises from a peptide derived from the amyloid precursor protein (APP) through a process of sequential cleavage brought forth by two enzymes: β-secretase 1 and γ-secretase. This process leads to the creation of peptides of anywhere from 36 to 43 amino acids. AD primarily involves the peptides of $A\beta_{40}$ and $A\beta_{42,}$ which are more prone to aggregation. Generally, Aβ is continuously generated and cleared under normal physiological conditions. Low picomolar concentrations of Aβ are even shown to enhance LTP and memory in hippocampus-dependent tasks **(Puzzo et al., 2008)**. However, in AD, the regular function is disrupted, leading to the accumulation of soluble Aβ oligomers, fibrils, and extracellular amyloid plaques.

Numerous studies show that Aβ oligomers are the most neurotoxic Aβ species compared to fibrils and plaques **(Selkoe, 2022; Koffie et al., 2011).** They accumulate at excitatory synapses and correlate with cognitive decline. Aβ oligomers disrupt synaptic plasticity through several mechanisms. One such mechanism involves glutamate dyshomeostasis **(Li et al., 2009; Palop and Mucke, 2010).** Glutamate dyshomeostasis is an imbalance in the levels of glutamate due to the lack of proper regulation. Glutamate is not only an important excitatory neurotransmitter responsible for neuronal communication but also an essential amino acid for the human body. Under regular physiological conditions, glutamate is regulated by glutamate transporters, proteins on astrocytes responsible for glutamate uptake, and glutamine synthetase, an enzyme that catalyzes the synthesis of glutamine from glutamate and ammonia. Aβ impairs glutamate uptake by reducing the transcription of important glutamate transporter proteins (GLT-1 and GLAST) on astrocytes, which damages their ability to remove glutamate from the synaptic cleft **(Li et al., 2009).** This results in an increased extracellular glutamate concentration, which leads to an overactivation

of NMDAR on the neurons, and the Ca^{2+} influx leads to excitotoxicity and dendritic damage. Additionally, the resulting excitotoxicity interferes with the signaling threshold for LTP.

Aβ oligomers are also involved in the disruption of AMPAR trafficking. They hijack endocytosis and sorting pathways, which leads to the rerouting of the insertion of AMPARs. This hinders the excitatory postsynaptic currents necessary for LTP. Without the ability for these signals to grow, LTP can not be carried forward. Earlier, this paper talked about how LTP under healthy conditions involved the insertion of AMPARs into the postsynaptic membrane to strengthen excitatory signalling. Aβ oligomers trigger the clathrin-mediated endocytosis (CME) of AMPARs. CME involves the transportation of molecules by vesicles coated with the protein clathrin. The disruption of AMPAR trafficking has a major impact on specifically E-LTP.

In addition to E-LTP, L-LTP is also affected by Aβ oligomers through the interference with gene transcription signalling pathways. Usually, the Ca^{2+} signals propagate into gene transcription mechanisms through kinase pathways. However, Aβ disrupts these kinase pathways and, in turn, disrupts the transcription of essential proteins. First, Aβ reduces CaMKII activation, which is essential for the phosphorylation of AMPARs to improve their glutamate sensitivity and promote their insertion. This results in lower AMPARs with the GLuA1 subunit, which are responsible for synaptic strength. Second, the PKA signalling pathways are also hindered. This pathway is really important because PKA translocates to the nucleus to activate CREB, which is essential for transcription. This means that there are lower levels of CREB, which reduce the synthesis of plasticity-related proteins (PRP) such as BDNF. Additionally, the MAPK/ERK pathway is also hindered, which leads to dendritic damage due to the lower amounts of BDNF, a PRP usually synthesized in these necessary pathways.

Neurofibrillary Tangles and Tau Protein

Tau is a microtubule-associated protein (MAP) that is important for the functioning of neurons **(Iqbal et al., 2005; Crews and Masliah, 2010).** Microtubules are cylindrical filaments that are composed of tubulin protein dimers. Their very dynamic nature allows them to be used for numerous functions in a cell, such as providing structure, transporting important cargo such as AMPAR/NMDAR and mRNA, and cell movement through cilia and flagella. They are especially significant in the transportation of signalling molecules in neurons. Under regular physiology, tau binds to β-tubulin, the protein that forms the structural backbone of microtubules. In AD, tau is hyperphosphorylated, which makes it detach from microtubule structures and aggregate into neurofibrillary tangles. These tangles are dangerous because they allow the tau to migrate from the regular axonal area to the dendritic areas.
The hyperphosphorylated tau, which can migrate to dendritic and spinal areas, disrupts the LTP and the mechanism of post-synaptic signaling **(Hoover et al., 2010; Spires-Jones and Hyman, 2014)**. This mislocalized tau is responsible for the removal of AMPARs from the postsynaptic neuron. As discussed previously in this paper, LTP requires the insertion of GLuA1-equipped AMPARs through CaMKII phosphorylation to amplify synaptic transmission. Spine tau promotes AMPAR internalization, shifting plasticity-related changes toward LTD-like changes as opposed to LTP.

Additionally, hyperphosphorylated tau separates from microtubules, which then are more susceptible to depolymerization **(Iqbal et al., 2005; Crews and Masliah, 2010)**. The depolymerization of these essential microtubules leads to the fall of the entire axonal transport system. This system is responsible for transporting mitochondria that supply ATP for cellular processes, vesicles containing important BDNF, and receptor cargo like AMPARs. Without this system, E-LTP, which functions with local proteins, receptors, and ATP, fails and diminishes the necessary effect of LTP.

Neuroinflammation Caused by Glial Dysfunction

Beyond amyloid-β and tau pathologies, scientists have determined that neuroinflammation poses a great problem in AD. Specifically, the neuroinflammation is caused by specialized glial cells known as microglia and astrocytes **(Heneka et al., 2015; Henstridge et al., 2019)**. In a healthy brain, astrocytes and microglia work to regulate neurotransmitter homeostasis, provide trophic support, and help clear extracellular debris. However, in AD, these cells become pro-inflammatory, releasing cytokines and reactive oxygen species (ROS) that interfere with synaptic signaling and plasticity. Cytokines are proteins that are key to immune responses in our bodies since they help immune cells interact and work together. Similarly, ROS are also signalling molecules in inflammatory responses, but ROS are toxic to DNA in high concentrations.

Pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) inhibit LTP **(Tong et al., 2012)**. While cytokine signaling can modulate synaptic plasticity under normal conditions, its elevation disrupts receptor trafficking and intracellular signaling. For example, IL-1β suppresses LTP by interfering with the CaMKII activation cascade and CREB-mediated transcription. Both of these processes are crucial parts of LTP.

Astrocytes add to this problem **(Hong et al., 2016; Heneka et al., 2015).** Normally, astrocytes are responsible for glutamate uptake in the synaptic cleft to regulate glutamate levels and avoid the overstimulation of receptors. In AD, glutamate transporters are downregulated significantly by amyloid-β oligomers, which hinders the astrocytes' function. The halted glutamate uptake results in excess glutamate and a resulting cascade of neuron damage through the overactivation of receptors and the influx of Ca^{2+}. The Ca^{2+} signaling disrupts the signaling required for LTP, shifting synapses toward LTD. Additionally, microglia play a role in this neuroinflammation. Persistent microbial activation leads to the release of ROS, which, as stated previously, causes damage to synaptic membranes and impaired mitochondrial function.

Together, these three processes establish a terrible cycle where amyloid-β and tau aggregates activate glial cells, which release inflammatory molecules. This further exacerbates synaptic dysfunction and loss of plasticity. Such an inflammatory environment prevents proper induction and maintenance of LTP, contributing to cognitive decline in AD.

THERAPEUTIC SOLUTIONS TO REPAIR LTP IN AD

Currently, scientists are exploring pathways to cure the pathological condition of AD. As discussed in this paper, AD has multiple mechanisms that ultimately work to inhibit physiological functions such as LTP. Therapeutic strategies have focused on targeting these distinct pathological processes to restore synaptic function. Each solution addresses specific molecular disruptions in AD, which highlights how complex and multifaceted the approach for curing AD is.

Substitute Agonists for BDNF-TrkB Pathways

Brain-derived neurotrophic factor (BDNF) is a crucial neurotrophin for sustaining neuron survival, synaptic plasticity, and learning-related processes (**Loprinzi, 2018)**. BDNF is a crucial PRP synthesized and used in LTP. BDNF exerts its effects primarily by binding to tropomyosin receptor kinase B (TrkB). TrkB is a type of enzyme that phosphorylates tyrosine residues on intracellular proteins after ligand binding. When BDNF binds to TrkB, multiple cellular pathways are activated, which contribute to neuronal function and synaptic strength. However, studies demonstrate that BDNF levels are reduced in the hippocampus of AD patients, correlating with cognitive decline and synaptic dysfunction **(Peng et al., 2005)**. Amyloid-β oligomers suppress BDNF expression and TrkB signaling, while tau pathology can disrupt the transport of BDNF.

In order to combat the lower levels of BDNF, a strategy of using 7,8-dihydroxyflavone (7,8-DHF), a small molecule that mimics BDNF, is employed to take advantage of the BDNF-TrkB pathways. By using a TrkB agonist, the beneficial impacts of the cascading pathways can be used to possibly cure the pathological damage caused by AD. A study by **Zhang et al.** showed that 7, 8-DHF prevented synaptic loss in mouse models of AD **(Zhang et al., 2014)**. Additionally, studies have proposed the use of gene therapy to employ a viral delivery of BDNF, but they have been limited due to safety concerns **(Nagahara et al., 2009)**. On the other hand, some studies have shown that non-pharmacological approaches can be successful (**Loprinzi et al. 2017). Loprinzi et al.** showed that chronic exercise led to an increase in BDNF and improvement in memory tasks.

PKR Inhibition

The protein kinase R (PKR) pathway is a crucial link between inflammation, amyloid-β toxicity, and synaptic dysfunction in AD. PKR is a kinase that is normally activated in response to cellular stress or viral infection. In AD, PKR is abnormally activated by proinflammatory cytokines and amyloid-β **(Peel et al., 2001; Hwang et al., 2017)**. These create a chronic stress environment at synapses. When activated, PKR phosphorylates the eukaryotic translation initiation factor 2 alpha (elF2α). This phosphorylation inhibits protein translation in neurons. As discussed previously, protein synthesis is essential for L-LTP. Also, PKR activation promotes pro-apoptotic signaling, which further impairs synaptic integrity and neuron survival **(Peel et al., 2001; Frey and Morris, 1997).**

Studies have shown that compounds that specifically inhibit the PKR kinase activity prevent the harmful elF2α phosphorylation. This, in turn, restores the protein translation required for L-LTP. In AD mouse models, PKR inhibitors have been shown to rescue synaptic plasticity in the presence of amyloid-β accumulation **(Hwang et al., 2017).** Additionally, genetic approaches such as reducing the expression of PKR have been shown to reduce elF2α phosphorylation **(Segev et al., 2015).** Targeting PKR alongside BDNF-based therapies may also enhance synaptic resilience.

Anti-Tau and Anti-Amyloid-β Immunotherapies

One of the most direct strategies for restoring synaptic plasticity in AD is by targeting the pathological proteins that disrupt synaptic function in AD: amyloid-β oligomers and hyperphosphorylated tau. These therapies use antibodies or vaccine-based approaches to neutralize and clear these toxic aggregates of protein. In turn, synaptic dysfunction is reduced, and LTP maintenance is promoted **(Spires-Jones and Hyman, 2014)**.

In regard to amyloid-β, scientists have developed a promising monoclonal antibody, aducanumab **(Palop and Mucke, 2010; Master and Selkoe, 2012).** Aducanumab binds specifically to amyloid-β aggregates in the brain. This binding then promotes phagocytosis through microglia. The process of microglial-mediated phagocytosis is when microglia engulf and eliminate cellular debris and pathogens. This function is essential for maintaining brain health during development. Microglial-mediated phagocytosis reduces the plaque load, which interferes with NMDAR and AMPAR function. Clearing the amyloid-β restores proper glutamate signalling, which enables the necessary Ca^{2+}-dependent kinase pathways in LTP.

Hyperphosphorylated tau forms neurofibrillary tangles that disrupt axonal support, as discussed previously. Anti-tau antibodies are expected to bind to these tangles and facilitate their clearance through microglial phagocytosis or endosomal-lysosomal pathways **(Iqbal et al., 2005; Cao et al., 2018).** By reducing the tau aggregates, anti-tau therapies seek to restore spinal structure and functioning and support LTP induction and maintenance. However, while aducanumab is approved by the FDA for clinical use, scientists are still testing anti-tau antibodies, so we do not have a specific antibody for tau yet. Additionally, clinical studies show that a simultaneous reduction of amyloid-β and tau results in a greater recovery of LTP, dendritic spine density, and memory performance than targeting only one protein **(Cao et al., 2018).**

CONCLUSION

This paper has talked about the basis of memory encoding through LTP and the pathological conditions of Alzheimer's Disease that affect the important process. Additionally, viable and promising directions for therapeutic solutions to restore synaptic plasticity in AD were discussed. I would like to point out that the field of neuroscience, especially in regard to AD, is very divided in which direction efforts to develop a

cure should go. Previously, scientists believed that PRPs such as BDNF and other related growth and repair pathways were the most important directions for a cure. However, in modern times, scientists have shifted towards the neuroinflammation side of AD. The popular belief is that immunotherapies, such as the glial cell therapies discussed in this paper, that target neuroinflammation are the most important therapies that must be worked on and improved. Additionally, debates about how to research AD have become more prominent. Currently, researchers have three main ways of studying AD pathology: human cases, mouse models, and, more recently, organoids. Organoids are miniature models of human organs grown from stem cells. Both of these debates show just how diverse the scientific community is regarding AD, but they also highlight the amount of progress that has been made and the amount of progress that is still left before we find a cure for AD.

While I understand why the field has shifted toward neuroinflammation, I think focusing on only one of these pathologies would be a mistake. As this paper has discussed, amyloid-β, tau, and neuroinflammation feed into each other, so a therapy that only goes after one of them would leave the other two to keep driving synaptic damage. As for the debate over model systems, I do not think it makes sense to pick one over the other. Mouse models are useful because they let researchers study AD in a living organism with a functioning immune system, which matters given how much neuroinflammation contributes to the disease. Organoids are useful because they are grown from human stem cells and can replicate human biology in ways that mice cannot. Future research should try to use both and connect findings across them rather than treat them as competing approaches.

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