

# Understanding the Effect of $\text{oA}\beta$ and $\text{oTau}$ Proteins on Impaired LTP Within Alzheimer's Disease

Shantala Totada<sup>1</sup> and Debra Abramov<sup>#</sup>

Liberal Arts & Science Academy High School, USA

## ABSTRACT

Alzheimer's Disease (AD) is associated with decreased memory recall, where synaptic plasticity is impaired between neurons. Synaptic plasticity is the ability to modify the strength or efficacy of synaptic transmission at synapses between neurons. One of the main forms of impaired synaptic plasticity includes long-term potentiation (LTP). Studies have shown that one of the main causes of the inhibiting LTP is through oligomeric amyloid-beta ( $\text{oA}\beta$ ) and oligomeric tau ( $\text{oTau}$ ) proteins.  $\text{oA}\beta$  was shown to impair glutamatergic synaptic transmission and subunit receptors including extrasynaptic NMDAR and NR2B respectively. Hippocampal slices were used and treated with CHO/7PA2 cells containing a V717F hAPP751 AD mutation.  $\text{oA}\beta$  was found to inhibit the extrasynaptic NMDARs along with the NR2B antagonists and produce impaired LTP. Using the extrasynaptic NMDARs was shown to dephosphorylate CREB, impairing LTP, not only in  $\text{oA}\beta$  but also in  $\text{oTau}$ . Additionally,  $\text{oTau}$  was shown to impair LTP through protein kinases GSK-3B and dephosphorylate tau through protein phosphatase PP2A, and  $\text{oTau}$  was able to impair LTP through tau isoform 4R/2N. Understanding the effect of oligomeric forms of protein aggregation within AD can help advance treatment development and use protein aggregation as a treatment.

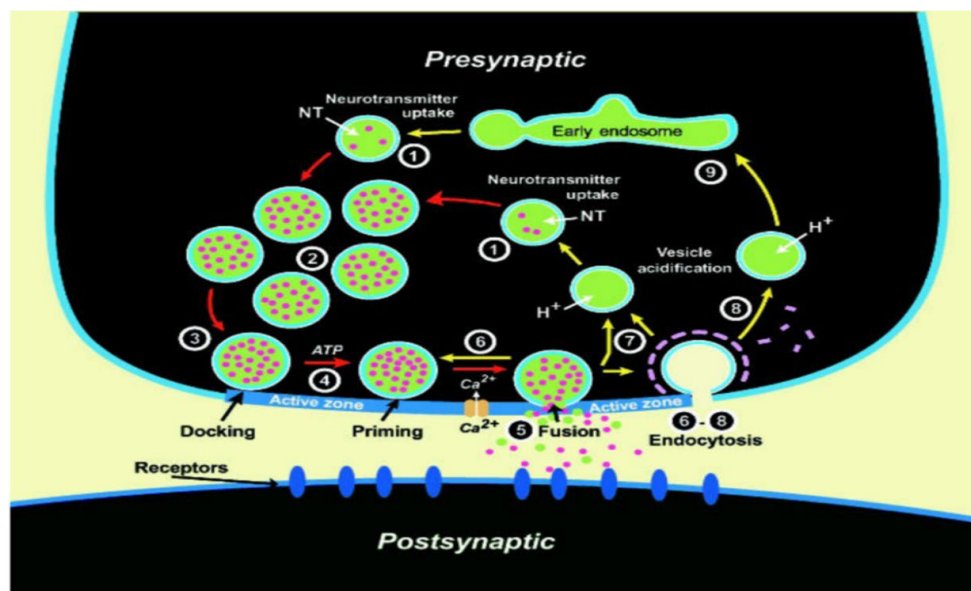
## **Introduction**

Alzheimer's Disease (AD) is a neurodegenerative disease that causes memory loss. It occurs mostly in adults older than 65 years of age and progressively gets worse with age. It is currently the seventh leading cause of death in the United States and the most common cause of dementia in older adults (*Alzheimer's Disease Fact Sheet* | National Institute on Aging, n.d.). Common symptoms of Alzheimer's patients include memory loss and loss of cognitive function, behavioral changes including depression, mood swings, loss of interest in activities, and aggression (Silva et al., 2019; Alzheimer's Disease - Symptoms and Causes - Mayo Clinic, n.d.). Currently, no treatment reduces or stops neurodegeneration, but certain medications alleviate the symptoms such as being forgetful, feeling confused, interacting with others, and feeling anxious (*Alzheimer's Disease*, n.d.). Research is ongoing to understand the disease further and develop therapies for AD.

Neurodegeneration is characterized by a wide range of issues including cognitive functions (memory and decision-making) and motor skills (*What Is Neurodegeneration?* n.d.). Neurodegeneration is the process where neuronal cells begin to degenerate or break down, lose their function, and ultimately die; this is a slow and irreversible process (Zvěřová, 2019). Neurodegeneration is primarily caused by pathological protein aggregation extracellular to the synapse. Because of the degeneration of neurons in areas of the brain responsible for learning and memory, the stimulus of an action potential is less resulting in a reduce neuronal communication.

An action potential occurs in the presynaptic terminal when a rapid change in membrane potential occurs within neural cells or muscle cells, allowing for communication between cells. To communicate, neurons must release neurotransmitters at their axons. First, neurotransmitters are packed into vesicles that are docked onto the active zone of the synapse and are primed to be released towards the post-synaptic neuron (Figure 1) (Südhof, 2004). One of the major neurotransmitters linked to learning and memory, glutamate, is released from

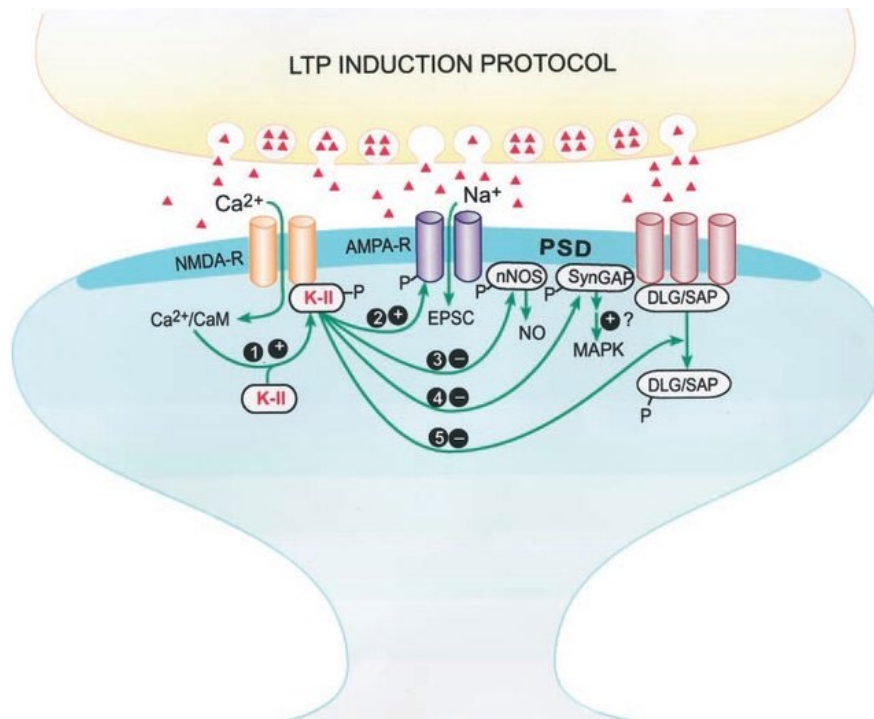
the synapse and binds to two glutamate receptors on the postsynaptic membrane: N-methyl-D-aspartate receptor (NMDAR) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA). AMPARs are ionotropic glutamate-gated ion channels that play a major role in synaptic transmission between synapses. NMDARs are ionotropic voltage and glutamate-gated ion channel located commonly on the postsynaptic membrane that is blocked by a  $Mg^{2+}$  ion and is highly permeable for  $Ca^{2+}$  (Chiu & Carter, 2022; Reiner et al., 2015).  $Na^+$  moves from the extracellular to the intracellular via AMPAR and  $K^+$  moves towards the extracellular component, resulting in stronger  $Na^+$  concentration and an increase membrane potential from resting potential (Hedges, 2022, 155). Once the postsynaptic membrane is sufficiently depolarized, the  $Mg^{2+}$  ion is released from the NMDAR on the postsynaptic, allowing for the flow of  $Na^+$  and  $Ca^{2+}$  through that channel. The influx of  $Ca^{2+}$  allows for more AMPAR production onto the postsynaptic cell membrane and an increased number of action potentials in the next cell via the action of calmodulin-dependent kinase II (CaMKII) (Südhof, 2004). When another action potential occurs, more glutamate can bind onto the increased quantity of AMPARs, resulting in a stronger communication between the pre- and post-synapse (Figure 2) (Hedges, 2022).



**Figure 1.** The synaptic Vesicle Cycle process starts from the uptake of neurotransmitters to the release of neurotransmitters via exocytosis; these neurotransmitters bind onto the receptors of the post-synapse and allow for depolarization (Südhof, 2004).

For effective neuronal communication and synaptic strength between neurons, synaptic plasticity is commonly referred. Synaptic plasticity is the “activity-dependent modification of the strength or efficacy of synaptic transmission at pre-existing synapses” (Citri & Malenka, 2007). Synaptic plasticity includes two different processes responsible for learning and memory: LTP (long-term potentiation) and LTD (long-term depression). LTP requires the activation of NMDARs in order to strengthen connections between neurons. LTD is the opposite process, where there is a high rise and low rise of  $Ca^{2+}$  concentrations that are regulated by NMDARs (Sumi & Harada, 2020). Less glutamate will bind the AMPAR and result in low levels of  $Na^+$  influx into the post-synapse via the AMPAR. While glutamate will bind to the NMDAR, there is insufficient depolarization to remove the  $Mg^{2+}$  ion (Südhof, 2004). Without the removal of  $Mg^{2+}$ , the calcium flow from the extracellular space towards the intracellular space will be less, making it more difficult to produce more AMPA receptors since calcium triggers the action of CaMKII, which is required to produce AMPAR via phosphoryla-

tion of the GluA1-Ser831 subunit (Citri & Malenka, 2008; Kristensen et al., 2011). When the number of AMPARs on the postsynaptic membrane is less, the synaptic connection between the pre and postsynaptic will be weakened (Südhof, 2004; Hedges, 2022).



**Figure 2.** CaMKII is in the postsynaptic density, producing more AMPA receptors (Soderling et al., 2001).

This review will go over how A $\beta$  is produced and how it causes protein aggregation leading to AD; additionally, hyperphosphorylation of tau proteins will be investigated to see their connection to AD. Protein aggregation of A $\beta$  and tau affects the balance between LTP and LTD in the hippocampus, namely upregulating LTD and downregulating LTP. Understanding the cellular and molecular mechanisms, including the balance between LTP and LTD, provides insight into one of the main causes of impaired cognitive function in AD patients.

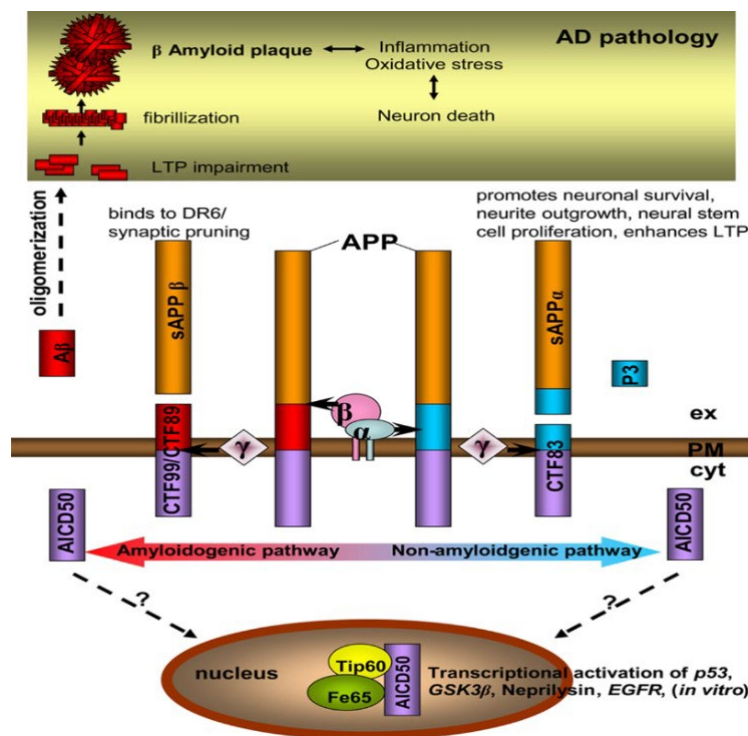
## Alzheimer's Disease

AD primarily affects neuronal communication within the brain, more specifically, the hippocampus. The hippocampus is responsible for converting short-term memories to long-term memory. When the synaptic strength increases, the hippocampus can store new memories, however, the presence of AD degenerates the neurons in the hippocampus (Hernández, n.d.; Kennedy, 2013). A $\beta$  is a 4kD peptide fragment, about 37 to 49 amino acids, and derived from the Amyloid Precursor Protein (APP), helps with neuronal growth and repair, but overproduction of it can form aggregates that affect neuronal signaling within the hippocampus and can contribute to impaired learning and memory.

APP is an extracellular, type 1 membrane glycoprotein that plays a major role in cellular functions such as the release of A $\beta$  (Chen et al., 2017; Hefter et al., 2020; Gralle & Ferreira, 2007). APP is located on the

postsynaptic densities and is partly responsible for synaptic plasticity and neuronal growth and survival (Benarroch, 2018). A $\beta$  is produced via sequential cleavage of APP by  $\beta$ - and  $\gamma$ -secretases (Cuestas Torres & Cardenas, 2020; Ma & Klann, 2012). APP starts in the plasma membrane, wherein a healthy neuron,  $\alpha$ -secretase acts upon it and cleaves it into secreted APP alpha (sAPP $\alpha$ ) and 83 amino acid C-terminal fragments (CTF83). CTF83 is then cleaved by  $\gamma$ -secretase, resulting in APP intracellular domain (AICD) which travels to the nucleus and affects transcription of proteins. The production of AICD is unaffected in Alzheimer's disease (Chow et al., 2010) (Figure 3.) sAPP $\alpha$  is secreted from neurons, which leads to positive synaptic plasticity, standard memory and thinking, neuronal survival, and regulated emotional behaviors. In some cases, APP is cleaved by the  $\beta$ -secretase enzyme to result in CTF99. The  $\gamma$ -secretase cleaves the CTF99 into AICD and A $\beta$  40/42 peptide.  $\beta$ -secretase enables A $\beta$  to be produced and accumulate within the hippocampus.

A $\beta$  contributes to synaptic plasticity by regulating the release of glutamate via the synaptic vesicle cycle using presynaptic alpha7 nicotinic acetylcholine receptors ( $\alpha$ 7nAChR) which have shown to play an important role in learning, memory, and attention (Benarroch, 2018; Lazarevic et al., 2017; Cuestas Torres & Cardenas, 2020; Levin, 2012). The process of A $\beta$  accumulation begins with A $\beta$  monomers that can assemble into either oligomer, protofibrils, or amyloid fibrils (Chen et al., 2017). Protein aggregation is the basis for the development of AD.



**Figure 3.** APP pathology and the products produced from the cleavages. Formation of A $\beta$  from APP pathology results in the use of  $\beta$ - and  $\gamma$ -secretase to produce A $\beta$  40/42 peptide (Chow et al., 2010).

### Soluble $\alpha$ A $\beta$ Impairs LTP

A $\beta$  40/42, which is A $\beta$  that contains 40-42 amino acids, acts with the apolipoprotein E (ApoE), which causes the aggregation of A $\beta$  oligomers creating amyloid plaque (Hampel et al., 2021). A $\beta$  monomers convert to a  $\beta$ -sheet-rich structure which further forms soluble oligomers which then advance into insoluble fibrils with the  $\beta$ -sheet structures as “seeds” (Kanekiyo et al., 2014). ApoE4 aggregates with A $\beta$ , forming large co-aggregates,

ultimately resulting in amyloid plaques within the hippocampus (Kanekiyo et al., 2014). Amyloid plaques are the pathological hallmark of AD, and these oligomers cause neuronal and synaptic dysfunction including impairment of LTP, mitochondrial dysfunction, and oxidative stress (Bode et al., 2017; Tolar et al., 2021).

Soluble oA $\beta$  is known to cause dysfunction within the synapses of AD and promote impairment in glutamatergic synaptic transmission, which involves NMDARs and glutamate subunit receptors (Danysz & Parsons, 2012). A study conducted by Li and her team attempted to understand the different forms of soluble oA $\beta$  from different sources including cultured cells, AD cortex, and synthetic peptides to stimulate extrasynaptic NMDAR and determine if impaired LTP exists using hippocampal slices. Slices were treated with a conditioned medium (CM) of Chinese hamster ovary (CHO) or 7PA2 cells containing V717F hAPP751 AD mutation that were harvested in a homogenization buffer and centrifuged at 10,000 x g for 15 minutes, resulting in the formation of a supernatant and pellet, defining them respectively as the extrasynaptic fraction and synaptic fraction. The soluble oA $\beta$  was found to inhibit the NMDAR-dependent hippocampal LTP due to the overactivation of the NR2B receptors, which are subunits of the NMDA glutamate receptor (Li et al., 2011). NR2B receptors commonly function in learning, memory processing, and pain perception and are involved with hippocampal LTD induction (Loftis & Janowsky., 2003; Zhao et al., 2005). They explored the soluble oA $\beta$  from CHO CM/7PA2 CM and discovered that LTP was inhibited in 7PA2 CM but not in CHO CM cells. Inhibition of LTP within 7PA2 was caused by what Li and her team described as low-n A $\beta$  oligomers. Another experiment within this study utilized NR2B antagonists were used on 7PA2 CM and CHO CM to examine if the inhibition of LTP does occur. As a result, overactivation of the NR2B NMDA receptor impaired synaptic plasticity by enhancing LTD. NR2B antagonists, however, were successful in preventing the inhibition of LTP on the oA $\beta$ , attributed to NR2B's structure (Li et al., 2011). A $\beta$  oligomers at low to sub-nanomolar concentration resulted in increased extrasynaptic NMDA response and this study also suggested that overactivation of NR2B receptors results in the extrasynaptic glutamate levels increasing because the soluble oA $\beta$  would impair the glutamate uptake (Li et al., 2009; Li et al., 2011).

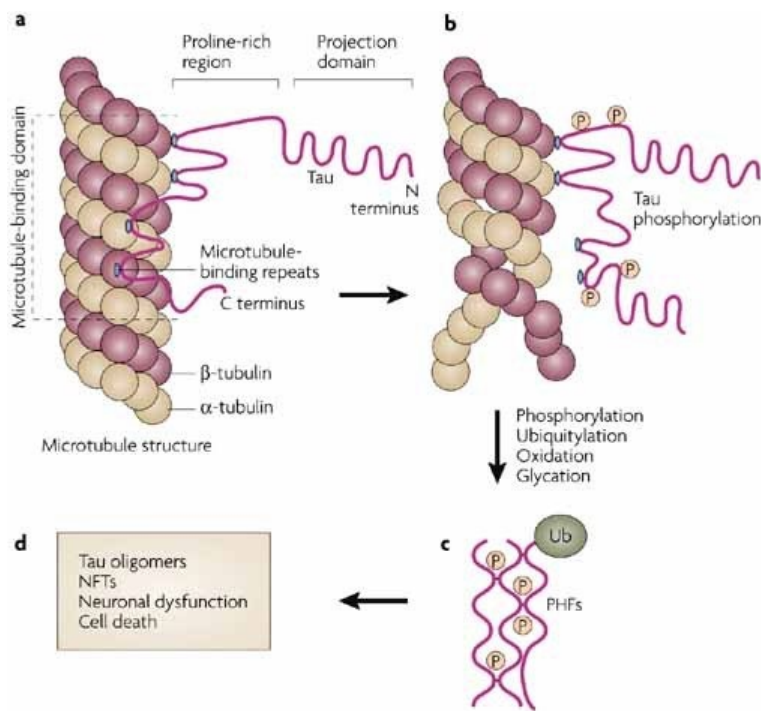
## **oA $\beta$ Uptake by Astrocytes**

Studies have shown that soluble oA $\beta$  facilitates the release of glutamate by activating astrocytes through  $\alpha$ 7nA-ChR, thereby enhancing the activation of extrasynaptic NMDARs (Talantova et al., 2013; Zhang et al., 2022; Frost & Li, 2017; Findley et al., 2019). The aggregation of extracellular glutamate induced by A $\beta$  is recognized as a detrimental upstream factor, which can also cause the overactivation of extrasynaptic NMDARs, ultimately leading to LTP impairment, LTD enhancement, and synapse loss (Huang et al., 2018; Zhang et al., 2022). The activation of extrasynaptic NMDA receptors allows Ca<sup>2+</sup> ions to enter the cell which results in ryanodine receptors to increase calcium-induced calcium release (Goussakov et al., 2010). This increases the number of intracellular Ca<sup>2+</sup> ions in the cell, leading to the activation of cAMP-regulatory element binding protein (CREB) shut-off pathways or dephosphorylation of CREB (Hardingham et al., 2002; Grochowska et al., 2022). CREB regulates the biochemical pathway that produces the synaptic connections between neurons, allowing for long-term memory formation (Tully et al., 2003). In a study done by Mun and her team, she explored astrocyte activation through oA $\beta$  using a primary astrocyte culture made from neonatal cerebral cortexes. When the astrocytes are activated, oA $\beta$  was able to induce apoptosis and an uptake of oA $\beta$  (Mun et al., 2024).

## **Hyperphosphorylation of Tau and oTau**

Tau is one of the proteins that greatly contributes to the progression of AD. Tau proteins are the subunit of the Neurofibrillary Tangles (NFT). Tau is a highly soluble and unfolded protein, that interacts with tubulin to help

assemble microtubules. Microtubules help contribute to the structures of neurons via reeling, a secreted glycoprotein that regulates the microtubule assembly and stability (Kolarova et al., 2012; Deutsch et al., 2006). Microtubules are found in all eukaryotic cells and are mainly composed of  $\alpha$ - and  $\beta$ -tubulin subunits which assemble to form linear protofilaments (*Microtubules: The Basics | Learn Science at Scitable*, n.d.). Other functions of microtubules other than maintaining cell structure include the assembly of spindle fibers during mitosis, cell division, cell motility, intracellular transport, and axon extension in neurons (*Microtubules: The Basics | Learn Science at Scitable*, n.d.; Alavi Naini & Soussi-Yanicostas, 2015). Microtubules are vital, especially for a neuron to be able to communicate and function effectively. Changes to the structure of tau proteins such as hyperphosphorylation can affect its role in the stabilization of the microtubules. When tau proteins are phosphorylated and form full-length monomeric forms of tau, the microtubules help provide stabilization for axons and dendrites (Robbins et al., 2021). Stabilization of the microtubules is also made possible by microtubule-associated proteins (MAPs) which bind to the microtubules and allow for more stability (Cooper, 2000). Tau is found in many places of a neuron including the endoplasmic reticulum, and even the Golgi apparatus (Ittner et al., 2010; Tang et al., 2015) (Figure 4.).



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**Figure 4.** Formation of tau proteins through microtubules composed of  $\alpha$  and  $\beta$ -tubulin. Tau oligomer formation is the result of hyperphosphorylation, and oligomers can form aggregates leading up to NFTs (Mazanetz & Fischer, 2007).

The hyperphosphorylation of tau aggregates to paired helical filaments (PHFs) which then create NFTs which are commonly found within the cerebral cortex which includes the entorhinal cortex, hippocampal formation, and neocortex (Furcila et al., 2019). Hyperphosphorylated tau is caused by an imbalance of protein

kinases and protein phosphate. Certain tau kinases include glycogen-synthase kinase-3B (GSK-3B), cyclin-dependent protein kinase 5 (cdk5), cAMP-dependent protein kinase (PKA), stress-activated protein kinases, mitogen-activated protein kinases (MAPK), CaMKII, and finally microtubule affinity-regulating kinase (MARK) (Medeiros et al., 2011; Gong & Iqbal, 2008). One kinase associated with LTD within the hippocampus is GSK-3B. A study done by Kimura and her team used MAPT<sup>+/+</sup> and MAPT<sup>-/-</sup> (microtubule-associated protein 'tau') mice to see if the protein kinase GSK-3B was used in the process of phosphorylation tau and regulating LTD (Kimura et al., 2014). GSK-3B is an isomer of GSK-3, a multifunctional serine/threonine kinase known to be a regulator of glycogen metabolism (Peineau et al., 2007). Kimura and her team used low-frequency stimulation (LFS) at 1Hz, 900 pulses within the CA1 dendritic region of the hippocampal slices. They incorporated a highly selective GSK-3B inhibitor called CT-99021 to determine if phosphorylation was due to the onset of GSK-3B during LTD. Through LFS, it was shown that the phosphorylation of tau with GSK-3B did play a role in the process of LTD (Kimura et al., 2014).

For protein phosphates, protein phosphatase 2A (PP2A) was commonly found to be associated with tau and AD. Dephosphorylation of tau is caused by PP2A (protein phosphatases 2A), the main phosphatase that accounts for 71% of the tau activity within the body (Wainaina et al., 2014). PP5 dephosphorylates hyperphosphorylated tau and when PP2 and PP5 are downregulated, it results in aberrant phosphorylation of tau (Wainaina et al., 2014).

Previous studies have linked tau aggregation and LTP. A study done by Fa and his team attempted to understand more about tau and LTP. (Fa et al., 2016). Fa and his colleagues used versions of the six isoforms of tau, which include N-terminus inserts, Exons 2 and 3, which result in 0N, 1N, or 2N, and isoforms 0N3R, 0N4R, 1N3R, 1N4R and 2N4R, with that being the longest tau totaling 441 amino acids. Fa and his team used mouse hippocampal slices and applied sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE) on those slices; SDS-PAGE is an electrophoresis method that separates the proteins dependent on their mass (Nowakowski et al., 2014). The SDS-PAGE gel was used in the sizes of the different isoforms of tau. When the 4R/2N isoform was applied, they saw a reduction in LTP. To provide more evidence based on this claim, oligomeric Tau (oTau) for 4R/2N isoform of tau was put into the dorsal mouse hippocampal area via the bilateral cannulas, a long tube used to inject chemicals into neuronal tissue (Czech & Stein, 1984). The addition of 4R/2N impaired contextual memory formation in mice; contextual memory refers to long-term memory, remembering emotional, social, spatial, or even temporal occurrences related to something (*Contextual Memory, Cognitive Skill*, n.d.) (Fa et al., 2016). Another methodology to test Tau on LTP was using soluble human AD-tau and adding it to hippocampal slices. As a result of this, the extracellular oligomer tau from AD patients created impaired LTP, supporting the overarching theme of oTau leading to LTP impairment (Fa et al., 2016).

Another study done by Acquarone and her team examined soluble oTau and its relationship with synaptic plasticity and memory in AD. CREB (cAMP responsive element binding) aids in an important role in memory retention (Acquarone et al., 2019). cAMP is activated through the activation of NMDA receptors and is partially responsible for inducing LTP. Acquarone et al explored the effect of upregulating the nitric oxide (NO) cascade, which is a part of the NO/cyclic guanosine monophosphate (cGMP) dependent protein kinases (PKG)/CREB pathway. The NO/cGMP/PKG/CREB cascade has certain therapeutic uses including erectile dysfunction and pulmonary hypertension (Acquarone et al., 2019). PKG is responsible for phosphorylating serine and threonine resulting in changes in the function of proteins and requires cGMP to function (Francis et al., 2010).

In Acquarone's study, she and her team upregulated the NO cascade onto the oTau using 3–4-month-old male and female C57BL/6 mice. Acquarone et al initially experimented with the suppression of CREB phosphorylation in animals who were exposed to oTau. CREB phosphorylation is vital for memory formation as it helps to promote the transcription of certain memory genes including cFos, Brain-derived neurotrophic factor IV (BDNF-IV), Early growth response protein 1 (EGR1), Arc, and Nr4a1 and Nr4a2 (Acquarone et al.,

2019). cFos is used for neuronal activity and is involved in certain biological processes including neuronal plasticity, cell growth, and mitosis (Barros et al., 2015; Velazquez et al., 2015). BDNF-IV regulates neuronal survival and growth, including axonal & dendritic growth and the synapse and participates in nerve plasticity which is important for memory formation and learning (Bach et al., 2023; Bathima & Das, 2015). The BDNF IV gene is used for certain cellular processes including protein catabolism and metabolism, and regulation of translation (Bach et al., 2023). The EDR1 gene is a part of certain processes including tissue injury, immune responses, and fibrosis (Wang et al., 2021). The arc gene is responsible for the endocytosis of AMPARs and is viewed as important for long-term memory formation (Korb & Finkbeiner, 2011). Nuclear receptor 4A1 (Nr4A1), also known as Nur77, and nuclear receptor 4A2 (Nr4A2), also known as Nurr1, are a part of the nuclear receptor protein family (NR4A) and regulate a variety of cellular functions including survival, inflammation, apoptosis, proliferation, metabolism, migration, autophagy, angiogenesis, and DNA repair (Odagiu et al., 2021; Zárrega-Granados et al., 2020).

**Table 1.** Table depicting the formation and effects of the protein aggregation forms of AB and Tau on LTP.

Protein formation types	Formation	Effect
Aβ Oligomers	Aβ monomers that clump together before they form amyloid fibrils	<ul style="list-style-type: none"> <li>• overactivation of the NR2B subunit of NMDA receptors</li> <li>• extrasynaptic NMDA receptors, the influx of Ca<sup>2+</sup> in the cell resulted in the CREB shut-off pathway</li> </ul>
Tau Oligomers	Hyperphosphorylation of tau and imbalance of the kinases and phosphates	<ul style="list-style-type: none"> <li>• Impair LTP through impairment of CREB phosphorylation and 4R/2N isoform of oTau</li> </ul>

## Discussion

One of the causes of the symptoms developed within Alzheimer’s disease is impairments of synaptic plasticity. As reviewed here, protein aggregation serves as a major factor for impaired synaptic plasticity, reducing the amount of LTP occurring within the neurons. The specific proteins involved in protein aggregation in AD include Aβ and tau, which form both monomers, dimers, and oligomers. Both proteins form oligomers that block LTP and prevent learning and memory from occurring as shown through the above studies conducted. Many of these studies used hippocampal slices of mice and a variety of experimental methods including electrophysiology and western blotting. Aβ dimers can inhibit LTP by themselves without the help of any other molecule as shown by Shankar and his team, and Aβ can produce cognitive deficits without the formation of protein aggregation. oAβ and oTau were also seen to inhibit LTP via their action on NMDAR and subunits of NMDARs. The interaction of oAβ with NR2B was found to impair LTP; this result was reinforced by the fact that the use of NR2B antagonists was required to protect against impaired LTP. NO was successful in protecting oTau from LTP impairment and is dependent on AD when aggregation occurs. cGMP was also able to fix impaired LTP due to CREB phosphorylation. The incorporation of the glutamatergic transmission of oAβ and oTau leading to impaired LTP provides researchers with insight into where to focus to develop a cure and what is necessary to attack protein aggregation within that specific area (Table 1). Additionally, the tau isoform 4R/2N was found to impair LTP and contextual memory through a study done on hippocampal mice samples using gel electrophoresis as one of the main processes. oAB and oTau aggregation has led to the development of AD through



impairing LTP. Studying protein aggregation as a cause of neurodegenerative diseases can provide compelling evidence to counteract the excessive growth of these proteins.

## Limitations

While these results provided insight regarding the process of impairment of LTP, questions remain on the line regarding the cellular and molecular mechanisms of AD and how there is not just one single cause for AD. Many signaling pathways that are involved in the development of AD and the production of  $\alpha\text{A}\beta$  and tau need to be explored rather than focusing on one source. Even though cellular and molecular mechanisms are studied, developing treatments for these proteins has not been actively explored and utilized by AD patients. More research is required to develop a functional treatment option for limiting protein growth and restoring LTP.

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