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GluN2B of NMDA receptor and Calmodulin: Ameliorate calcium homeostasis for the mitigation of Alzheimer disease

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ABSTRACT
N-methyl-d-aspartate receptor (NMDAR)mediated excitatory glutamatergic neurotransmission is essential for synaptic plasticity and neuronal survival. However, excessive NMDAR activation results in excitotoxicity and encourages cell death as well as providing a probable explanation for the development of Alzheimer's disease (AD) like pathology. It's possible because of Mg2+ ions, which block NMDA receptors while at rest and are unable to do so under synaptic plasticity. Earlier studies have reported that blocking NMDAR by Mg2+ can improve AD. Further, calcium homeostasis can be another convincing explanation for AD. Thereby calcium plays an etiological factor in synaptic plasticity and can cause Alzheimer disease. According to studies, calcium homeostasis is maintained by calmodulin, however, calcium imbalance because of calmodulin can result in excitotoxicity. Additionally, the endoplasmic reticulum can disturb the body's calcium homeostasis by malfunctioning mitochondria..An attempt has been taken to review the different subunits of NMDA receptors, Calmodulin and Mitochondrial calcium release their physiological roles to understand the possible etiological causes for the mitigation of AD.

Keywords: Alzheimer, NMDA, GluN2B receptor, Ca++ ions, Aßplaques, Calmodulin, Neurofibrillary tangles

I. INTRODUCTION

Alzheimer's disease (AD) is a disease that is related to age. The characterization of the disorder is cognitive dysfunction, memory loss, and some changes in behavior and personality [1-2]. Two different types of AD have been established. One AD is familial whose origin is genetic, and the other is sporadic AD. Sporadic AD is a common type of AD that occurs in humans. It is difficult to distinguish between the two types of AD but some novel studies suggested that uptake of glucose, signaling of insulin and metabolism could be the factors for the pathogenesis of sporadic AD [3]. The accumulation of neurofibrillary tangles and Amyloid-plaques is one the reasons for AD. Amyloid Precursor Protein (APP) are the precursor protein of A**β** (peptide) which in turn undergoes cleavage by amyloidogenic and non-amyloidogenic proteins[4-6]. The only protein present in the neuronal axon of a healthy brain is Tau. It is hyperphosphorylated in the AD brain and forms neurofibrillary tangles. Neurofibrillary tangles occur in most locations in the brain as the pathology of AD[7]. One reason for neurodegenerative disorders like AD is the overactivation of NMDA receptors which causes excitotoxicity to the neurons[Liu Z 2020]. In neurons a crucial cellular messenger is calcium. Amyloid plaques and neurofibrillary tangles can develop as a result of a disturbance in calcium homeostasis. [Joshi M 2022]. Excessive calcium entry through NMDA receptors is the principle mediation for toxicity as NMDA has more permeability for calcium ions than any other iGluR[8]. Glutamate is a neurotransmitter binds to ionotropic receptors like the NMDA receptor which is calcium permeable.Inexcitotoxicity, there is impaired glutamate transported function which results in the elevation of glutamate which may leads toa significant increase in sodium and calcium. Sodium causes inflammation in the neurons and calciumleads to excitotoxicity[9-12]. Thus, for the development of neuroprotectants, the NMDA receptor is one of the proposed therapeutic targets [13]. Here some of the etiological and pathophysiological factors are associated with AD have been summarized.

Role of Amyloidosis in AD

Amyloidosis is a clinical and pathological disorder wherein the body's tissues and cells accumulate amyloid, leading to amyloid plaques for a variety of complex causes of organ failure in the long run [14]. It is the primary factor that has been identified as the major factor that leads to the pathogenesis of Alzheimer's key is amyloid peptide Aβ

[15].High levels of the transmembrane protein amyloid precursor protein (APP) which has

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extracellular domains are found in the brain. [16-17]. By controlling synaptic plasticity,the APP and its non-amyloidogenic cleavage products, particularly soluble APP have a physiological role in neuroprotection [18]. Though, Aβ is produced when two hydrolyses including secretase internal and extracellular cleave APP[19].

Normal APP processing involves constitutive and controlled cleavage by secretase which is not amyloidogenic [20].Proteins that are misfolded and have a persistent secondary structure are called amyloid proteins[14]. The successive cleavage of APP in a sick condition result in the production of a polypeptide with 39 to 43 amino acid residues [21]. The two primary peptide subtypes, A40 and A42. Each have 40 and 42 amino acids respectively and directly contribute to the development of neurotoxicity [22-23].

There are several different forms of A40 and A42 including monomers, soluble oligomers, protofibrils and insoluble fibers [24]. Patients with PD and traumatic brain injury both have an accumulation pointing to a link between amyloid and neurodegenerative illnesses [25]. Furthermore, there are several literatures revealed that both intracellular and extracellularprevents longterm potentiation, increases synaptic dysfunction, multiplies oxidative stress and neuroinflammation, activates tau phosphorylation, degrades neuronal health, and eventually leads to neuronal death. [26-28]. Fig 1 demostrates the steps for the formation of Amyloid-beta fibrils from Amyloid precursor Protein.

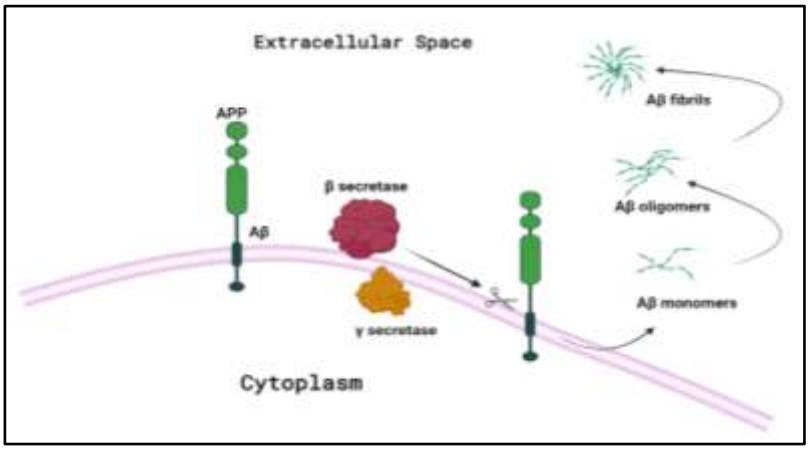

Fig:-Formation of Amyloid-beta fibrils from Amyloid precursor Protein

Senile Plaquesand AD

Aggregates of the tau protein and microtubule related proteinare the second main pathological finding in AD [Wood JG, [29]. Extracellular amyloid deposits known as senile plaques are present in the brain which are the most prominently cases of AD[30]. The pathogenic function of neurons, astrocytes, microglia, and capillaries in the development of AD has been the subject of recent investigations [31-33].

NMDA and its association with Ca2+

Three distinct subunits known as GluN1, GluN2, and GluN3 make up the NMDA receptor family [34].There are four (GluN2A-D) and two (GluN3A and Glu3B) genes that encode the GluN2 and N3 subunits, respectively [35].Two mandatory GluN1 subunits are combined with two GluN2 and/or GluN3 subunits to form heterotetramers that make up functional NMDA receptors [36]. All of the subunits have a high degree of structural similarity and homology, and their domain organization is retained. The extracellular ion channel is made up of a transmembrane domain (MD), an extracellular amino-terminal domain (ATD), and an extracellular ligand binding domain (LBD) [37]. The GluA2 subunit of AMPA receptors must bind glutamate in order for NMDA receptors to open, and depolarization removes Mg2+ blockage. Ca2+ entrance and action potential propagation are made possible by postsynaptic NMDA receptors [38**]**.Ca2+channels open, allowing for Ca2+ inflow and glutamatergic vesicle exocytosis.Glutamate is converted to glutamine in astrocytes by the enzyme glutamine synthetase, which is then transported back into glutamatergic neurons where it is digested into glutamate[39]. In the synaptic cleft, glutamate is released and binds to synaptic receptors. So, with the agreement of the above findings researchers reveled that glutamate is

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absorbed by astrocytes through EAAT1/2 (excitatory amino acid) and stored in vesicles. The activation of neuronal survival is triggered by Ca++ influx through synaptic NMDA receptors, whereas Ca++ influx through other synaptic receptors relates to cell death [40-41].CAM/ERK/CREB signalling pathways controlling transcription in neuronsElevating CREB promotes memory enhancement and neuronal protection. Extrasynaptic NMDA NR2B receptor activation inhibits the CREB-regulated pathway, increases ROS, causes mitotoxicity, and triggers apoptosis[42]. Structure of NMDA is illustrated in Fig.2

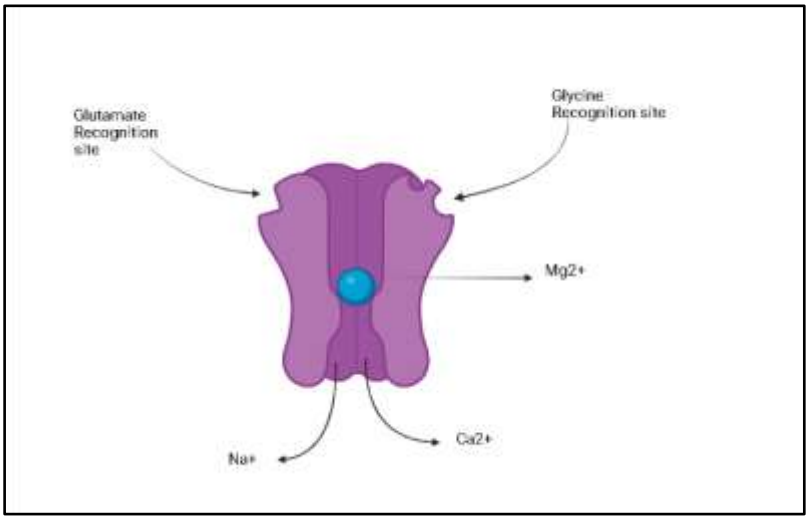

Fig. 2:- This shows the structure of NMDA receptor and the binding sites of the receptor. Here $Mg2^+$ is released when the NMDA receptors are activated and leads to release of Ca2+ and Na^+

Activation of NMDAr and Aβ synthesis

Extrasynaptic NMDA receptors must be activated in order to produce Aβ, and vice versa, Aβ accumulation also activates extrasynaptic NMDA receptors. [43].Numerous investigations have demonstrated a connection between NMDAR activation, APP processing, and the generation of neuronal Aβ. The synthesis and release of Aβ were initially shown to rise with sustained stimulation of cortical neuron cultures with a sublethal dose of NMDA [44]. NMDAR activation boosted non-amyloidogenic -secretase-mediated APP processing following glutamate or NMDA therapy [45].Increased -secretase-mediated cleavage of APP is the primary cause of NMDAR-mediated suppression of A release. Prior research has shown that the putative -secretases ADAM10 and ADAM17 compete with one another to cleave the APP. [46]. Therefore, a rise in -secretase-mediated APP cleavage in response to NMDAR activation would decrease the quantity of APP accessible for BACE1 cleavage and hence decrease the generation of neuronal Aβ [47].In addition, extrasynaptic NMDA receptor stimulation causes tau to be overexpressed and phosphorylated, resulting in neurofibrillary tangles[48].

However, Aβ interaction with NMDA GluN2B receptors significantly increases Ca2+ instantly**[**49]. Elevated Aβ has been shown to disrupt NMDA receptor function, Ca2+ homeostasis and early cognitive impairments. These effects may be increased by treatment with GluN2A antagonists[50]. So these strategies may be an useful biomarkers for the management of neurodegeneration.

Impact of NMDA and Calcium ions for the mitigation of AD

The primary excitatory neurotransmitter present in the human brain is glutamate which is regulated by N-methyl-D-aspartate which is a receptor. NMDA is activated by the release of glutamate at presynapse and the depolarization of the postsynaptic membrane to free the channel blocked with Mg2+[1]. Different NMDAR subunits have been identified such as the GluN1 subunit, four different GluN2 subunits like GluN2A, GluN2B, GluN2C, GluN2D, and a pair of GluN3 subunits such as GluN3A and GluN3B[51)]. Among the ionotropic glutamate receptors, NMDA has the highest calcium permeability. It includes two GluN1 and two GluN2 subunits and one

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GluN2 subunit is superseded with GluN3. The heteromeric NMDA receptors are congregated by two GluN1 and two GluN2 subunits of the same type like GluN2A/GluN2A and on the other hand triheteromeric, NMDA receptors are congregated with two GluN1 and two different GluN2 subunits like GluN2a/GluN2b[52],

GluN2A and GluN2B subunits are present in cortical, hippocampal and striatal neurons of rodents. For younger rodents, GluN2D is present in the hippocampus but in adulthood, the subunits are not detectable[51].For neuroplasticity and LTP processes, the NMDA receptor must be physiologically stimulated[52].At the cellular level, synaptic plasticity, which is known to be the fundamental basis of learning and memory processes, manifests itself in two ways: long-term potentiation (LTP) and long-term depression (LTD)[53-54]. AMPARs andNMDARs are important players. in controlling LTP and LTD. When glutamate levels are too high, NMDA receptors are continuously stimulated and this causes a significant influx of calcium ions into the cell. [55].When the set of biochemical processes leading to LTP start depends on how much Ca2+ calcium ions are let into the cell via open NMDA channels. [56].A, a strong neurotoxic peptide, may activate NMDARs to enhance the excessive intake of calcium ions (Ca2+), cause the internalisation of NMDARs and AMPARs, which suppresses LTP and promotes LTD, and also function as a signal for these receptors to internalise and ultimately resulting in synaptic damage and the impairments in learning and memory recognised in AD [57-58].According to studies, Aβ and hyperphosphorylated tau work together to promote oxidative stress, an increase in the generation of reactive oxygen species (ROS), and NMDAR-mediated synaptotoxicity. [59].Recent research demonstrated that tau phosphorylation and synaptic dysfunction are intimately associated to NMDAR activation, excessive Ca2+ influxes, and free radical production[60]. The association between NMDA and Ca2+ have been depicted in the figure number **3.**

Physiological processes including cell proliferation, metabolism, muscular contraction, bone growth, control of gene expression, and pathophysiological processes like metastasis and death all depend on calcium [61].Regulation is required because, under some clinical circumstances, increased calcium channel expression disrupts calcium homeostasis. CCBs, in the ideal scenario, may offer this regulation[62].In addition to their usual activities, CCBs are reported to have positive effects on the cognitive profile of the older population and individuals with diseases such as Parkinson's, diabetes, hypertension, and Alzheimer's disease. [63-65].

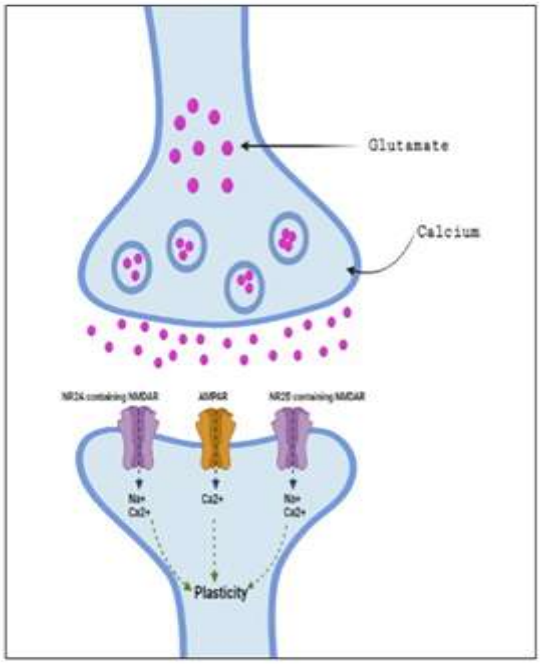

Fig. 3: This figure illustrates how glutamate is produced and how it binds to the NMDA receptor to release Na+, Ca2+, and other cations, leading to synaptic plasticity

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GluN2A receptor

An external N-terminal domain (NTD), a transmembrane domain (TD), and an intracellular C-terminal domain (CTD) are present in all NMDAR subunits [66-68]. Interactions between proteins at the GluN2A CTD are most likely to blame as GluN2A-containing NMDARs are move less quickly at synapse than GluN2B-containing NMDARs. [69].High sensitivity to Mg2+ is the first distinctive channel property that GluN2A gives to NMDARs[70].Since GluN2A-containing NMDARs have unique channel characteristics that produce unique calcium dynamics in the postsynapse, the GluN2A subunit has been the subject of extensive research. GluN2A CTD enables a distinct intracellular molecular association with proteins, such as kinases, phosphatases, and synaptonuclear transmitters, which inherently regulate plasticity signaling. [71-73]. Recently, the role of the GluN2A subunit in AD has been considered as another potential pharmaceutical target. In specifically, it was shown that GNE-0723, a novel positive allosteric regulator of GluN2A-containing NMDAR, may help with cognitive impairments in a mouse model of AD (J20). [74].

GluN2B receptor

In both normal and abnormal states the excitatory transmission of synaptic information, plasticity, and excitotoxicity, the CNS's NMDA receptors are essential. [75]. The depolarization of neurons and subsequent Ca2+ influx could be caused by glutamate's excessive activation of NMDA receptors. A number of Ca2+-dependent enzymes are activated by intracellular Ca2+ overaccumulation, and these enzymes may result in neuronal injury and death [76]. The selective inhibition of NMDA receptors, including those comprising the GluN2B subunit, is a successful strategy for decreasing the adverse effects of excitotoxicity in many illnesses, including Alzheimer's disease. [77-78].

ACh levels and cholinergic transmission are now maintained by either reducing acetylcholinesterase (AChE) to ease symptoms, or by controlling the activation of NMDA receptors. The only approved medications for the symptomatic alleviation of mild to moderate AD are three AChE inhibitors, including donepezil, rivastigmine, and galantamine, and one noncompetitive NMDA receptor antagonist Memantine.Currently, therapies for AD either reduce symptoms by controlling NMDA receptor activation or by blocking acetylcholinesterase to maintain levels of acetylcholine and cholinergic transmission. Additionally, there are only three AChE inhibitors—donepezil, rivastigmine, and galantaminehat are licenced for the symptomatic alleviation of mild to moderate AD as well as one noncompetitive NMDA receptor antagonistas therapeutic alternatives for the treatment of AD [79-80]. Recent research has shown that the crucial function that GluN2B-containing NMDA receptors play in synaptic plasticity in the regulation of learning and memory [81]. In AD models, it has beendemonstrated that GluN2B subunit expression decreases with aging, corresponding with weakened long-term potentiation (LTP) as well as a deterioration in cognitive performance. [82]. Traxoprodil and other selective GluN2B antagonists have previously enhanced task performances and increased impulsive type reactions in several animal experiments, suggesting their potential role as cognitive enhancers in AD [83].

Role of calcium in Alzheimer's

Variation in the level of calcium can regulate both information and storage which is required for proper cognition. The up-regulation of calcium signaling increases the expunction of normal memory and leads to progressive memory loss. During the day time, the activation of long-term potentiation (LTP) and aid in memory storage are both facilitated by the high concentration of calcium.. In the course of a certain phase of sleep, the temporary memory develops into permanent memory and in another phase of sleep the memory is erased by arousing long-term depression (LTD). But in AD patient, overexpression of calcium erases the memory from the temporary memory itself [84].

The initiation of LTP leads to drawing out the release of glutamate that in turn activated AMPA receptors and leads to depolarization. This depolarization state abolishes the blockage of magnesium and results in calcium influx. LTP depends on an increase in calcium influx whereas LTD depends on lower calcium influx and perisynaptic NMDAR’s activation. The blockage of magnesium may be related to increased accumulation of Aß. the accumulated Aß changes the NMDAR pathway to the pathway which is involved in LTD and leads to loss of synapse. LTP is affected by Aß accumulation and enhanced LTD by the same [1].

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Calmodulin(CaM) regulation of LTP and LTD

A conformational change takes place by increasing calcium ion concentration in the local post-synaptic region which in turn binds and activates CaMKII. It is an important step in LTP. On the contrary, CaM instead of activating CaMKII activated CaN (Calcineurin) which is an important step of LTD. To regulate the events of CaMKII, CaN, and other calmodulin-binding proteins (CaMBPs), CaM is a limiting factor. Calpacitins is a CaMBPs present in postsynaptic that binds with apo-CaM which limits the ability of CaM to activate CaMBPS [85].

NMDA-type receptors for glutamate (NMDARs) activate CaMKII at the hippocampus CA 3 to CA1 synapse which then potentiates AMPAR currents via a number of different pathways. Two additional CaMKII mechanisms and GluN2B binding are necessary for the entire increase of glutamate receptor function during LTP, in addition to Ca2+/CaM stimulation [86].

Neuropathological hallmarks of AD include tau and Aß peptides; tau, amyloid precursor protein, and beta-site APP-cleaving enzyme 1 (BACE1) are CaMBPs.Tau is a member of the family ofmicrotubule-associated proteins, which are involved in microtubule stability and assembly. Microtubule-associated protein 2 and tubulin are further CaMBPs [87-88]. Additionally, CaM binds to and controls the activity of a number of protein kinases involved in the hyperphosphorylation of tau, includingCaMKII, cyclin-dependent kinase 5, and glycogen synthase kinase 3[89-90]. CaM interacts with mGluR5 and then controls the movementof the receptor [91-93].The kinase could interact with mGluR5 till it is active, and it also appears that CaMKII mediates cross-talk across the two receptors, prompting the enzyme to dissociate and subsequently attach to a nearby NMDAR GluN2B subunit[94].These two crucial AD receptors are connected to CaM in several ways, all of which are impacted by Aβ oligomers. The number of The number of effective CaM and CaMBP antagonism and inhibitors has grown, expanding the extensive list that researchers studying Alzheimer's disease can use right now[95-96].It has also been demonstrated that CaM targeting drugs is safe for human consumption. Pancreatic cancer and cancer-dependent processes like angiogenesis have both recently been effectively treated with CaMantagonists[97].

Ca2+ in the mitochondria is harmed just by the presence of Aß. In vitro mitochondrial Ca2+ uptake and overload are caused when soluble A oligomers (Ao) are directly exposed to neurons. The permeability transition pore (mPTP), the release of cytochrome c, and apoptosis are all triggered by this rise in mitochondrial Ca2+[98-99]. It's been hypothesized that A interacts with CypD, a mPTP regulator, to open the mPTP, which causes depolarization, a reduction in the capacity of mitochondrial Ca2+ buffering, and a rise in the generation of ROS, all of which cause damage to neurons and a decline in cognitive function [98].According to the calcium hypothesis of AD, abnormalities in neuronal calcium signalling are responsible for both the buildup of amyloid plaques and a number of biochemical alterations within the cell that lead to neuronal dysfunction[99].Only 2% of a person's total weight is made up of the brain, yet it consumes 20% of the body's oxygen[100].All neurodegenerative disorders, including Alzheimer's disease, have mitochondrial dysfunction[101].Other investigations have demonstrated that increased ER or cytoplasmic calcium triggers the phosphorylation of APP and tau, increasing Aβ beta synthesis. This suggests that intracellular calcium dysregulation exacerbates the pathophysiology of amyloidosis and tau[102].Mitochondrial function is significantly impacted by intracellular calcium. The tricarboxylic acid (TCA) cycle and the electron transport chain are both directly stimulated by calcium, which results in an increase in oxidative phosphorylation[103-104]. By securing and buffering cytosolic calcium, mitochondria in turn control cellular calcium signalling. calcium transport into the mitochondria is made easier by MAMs(Mitochondrial membrane). An increase in cytosolic calcium can encourage the absorption of calcium into the mitochondria since MICU1 and MICU2/3 are capable of calcium sensing and gating. [104-107].Additional research showed that Aβ oligomers encouraged the release of ER calcium, which increased the amount of mitochondrial calcium and caused dysfunction in the mitochondria. [108].It has been demonstrated that abeta exposure increases the amount of mitochondrial calcium in cortical neurons, which causes neurodegeneration and may be prevented by inhibiting MCU[109]. **Fig.4** represents various factors cause NMDA activation and inturn leads to synaptic toxicity and amyloid plaques due to oxidative stress. Through the increased generation of reactive oxygen species (ROS), it has also been demonstrated that increased mitochondrial calcium impairs neuronal function[110].ROS are a consequence of the reduction of oxygen, and they

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are a main source of ROS in mitochondria[111].The relationship between oxidative stress and mitochondrial dysfunction is strong because dysfunctional mitochondria produce more ROS in turn. It has long been hypothesised that Increased ROS brought on by a dysfunctional electron transport system or a malfunction of the antioxidant system accelerates cellular damage brought on by ROS, leading to aging. [112-113].Aβ plaque development is preceded by increased ROS, which has a strong correlation with the early stages of AD[114].Additionally, it has been demonstrated that mitochondrial calcium influx causes by encouraging oxidative phosphorylation in cells and raising the amount of ROS generated as a result, it might cause mitochondrial damage. [115-116]. Fig.4 illustrates damaged mitochondria leads release of calcium from ER and intuen leads to disregulation of calcium level and cause excitotoxicity. Fig 5 demonstrates the pathway for the formation of neurofibrillary tangles and plaques.

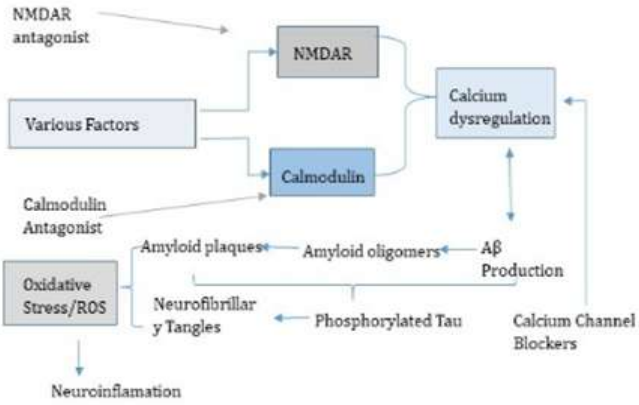

Fig.4:- This demonstrates how a variety of things affect NMDAR and calmodulin, which in turn affects calcium homeostasis and quickly produces Aβ and Tau. ROS are produced as a result of Aβ and Tau, which causes neuroinflammation.

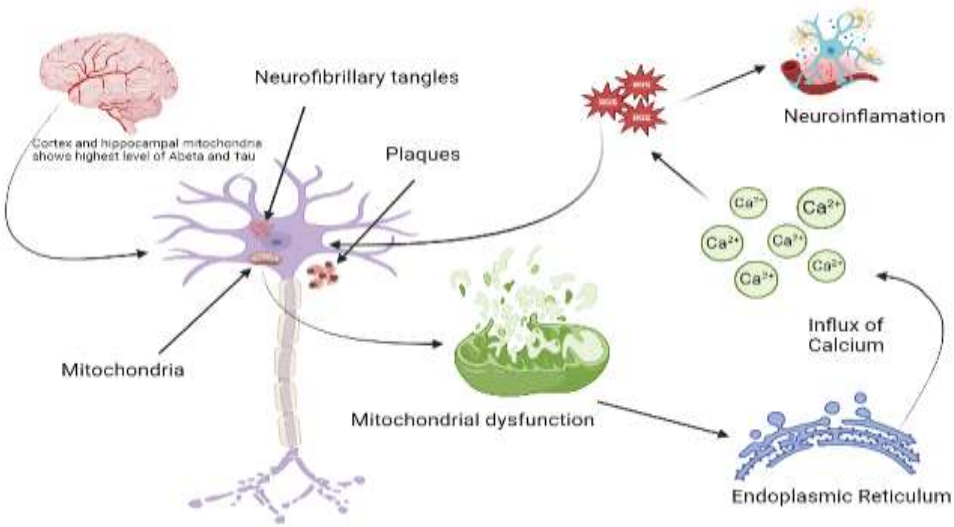

Figure 5: This demonstrates how damaged mitochondria in the cortex and hippocampus regions may release calcium from the endoplasmic reticulum, create ROS, and affect the production of amyloid beta, which can result in excititoxicity or neuroinflammation.

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II. CONCLUSION

Alzheimer disease is a progressive neurodegenerative disease which commonly occurs in elderly peoples and are characterized by dementia. There are various probable cause for Alzheimer such as Acetylcholine depletion, over activation of NMDAR, Oxidative stress, Amyloid plaques, Neurofibrillary tangles.The body's calcium homeostasis is kept in check by NMDA, Calmodulin, and mitochondrial calcium released by the ER. However, their dysregulation can affect the body's calcium homeostasis and produce excitotoxicity, which in turn harms neurons and causes neuroinflammation. One of the probable treatments for Alzheimer disease can be regulation of Calcium homeostasis in body. This can be achieved by blocking GluN2B receptors which is a subunit of NMDARs. Also, it can be achieved by regulating the calmodulin (CaM) which also regulates LTP and LTD. LTP and LTD are important for memory function. Mitochondrial dysfunction from ER also leads to calcium dysregulation which could be another probable reason to generate ROS and leads to AD . So considering the above pointed scientific inputs an attempt has been taken to establish the relationship between NMDA and $Ca2^{+}$ ion to find out the possible challenges and treatment strategies to overcome the AD.

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