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Mechanism of Oxidative Stress and Synapse Dysfunction in the Pathogenesis of Alzheimer's Disease: Understanding the Therapeutics Strategies

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Abstract

Synapses are formed by interneuronal connections that permit a neuronal cell to pass an electrical or chemical signal to another cell. This passage usually gets damaged or lost in most of the neurodegenerative diseases. It is widely believed that the synaptic dysfunction and synapse loss contribute to the cognitive deficits in patients with Alzheimer's disease (AD). Although pathological hallmarks of AD are senile plaques, neurofibrillary tangles, and neuronal degeneration which are associated with increased oxidative stress, synaptic loss is an early event in the pathogenesis of AD. The involvement of major kinases such as mitogen-activated protein

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kinase (MAPK), extracellular receptor kinase (ERK), calmodulin-dependent protein kinase (CaMKII), glycogen synthase-3β (GSK-3β), cAMP response element-binding protein (CREB), and calcineurin is dynamically associated with oxidative stress-mediated abnormal hyperphosphorylation of tau and suggests that alteration of these kinases could exclusively be involved in the pathogenesis of AD. *N*-methyl-D-aspartate (NMDA) receptor (NMDAR) activation and beta amyloid (Aβ) toxicity alter the synapse function, which is also associated with protein phosphatase (PP) inhibition and tau hyperphosphorylation (two main events of AD). However, the involvement of oxidative stress in synapse dysfunction is poorly understood. Oxidative stress and free radical generation in the brain along with excitotoxicity leads to neuronal cell death. It is inferred from several studies that excitotoxicity, free radical generation, and altered synaptic function encouraged by oxidative stress are associated with AD pathology. NMDARs maintain neuronal excitability, Ca^{2+} influx, and memory formation through mechanisms of synaptic plasticity. Recently, we have reported the mechanism of the synapse redox stress associated with NMDARs altered expression. We suggest that oxidative stress mediated through NMDAR and their interaction with other molecules might be a driving force for tau hyperphosphorylation and synapse dysfunction. Thus, understanding the oxidative stress mechanism and degenerating synapses is crucial for the development of therapeutic strategies designed to prevent AD pathogenesis.

Keywords

NMDA receptor; Oxidative stress; Kinases; Tau protein; Synaptic function; Alzheimer’s disease

Introduction

Alzheimer’s disease (AD), the most common neurodegenerative disorder, is characterized by deposition of amyloid-beta plaques (Aβ), neurofibrillary tangles (NFTs), and hyperphosphorylated tau (a microtubule binding protein) [1]. It has been reported that impairment of amyloid precursor protein (APP) metabolism in AD leads to increased production of Aβ. A high level of Aβ production is directly correlated with other critical events such as formation of tangles, neuron loss, synapse loss, and neurotransmission dysfunction [2] (Fig. 1). Interestingly, these changes are associated with *N*-methyl-D-aspartate receptor (NMDA) receptor activation and oxidative stress which ultimately results in AD pathology. Besides, Aβ is also reported to trigger NMDA-mediated Ca^{2+} influx, excitotoxicity, and stress-related signaling pathways in neurons which may exacerbate aging-related increases in oxidative stress, impaired energy metabolism, and defective Ca^{2+} homeostasis [3]. The NMDA receptors (NMDARs) are cationic channels gated by the neurotransmitter glutamate having critical roles in excitatory synaptic transmission, plasticity, as well as in excitotoxicity in the central nervous system (CNS). The activation of NMDAR glutamate release leads to massive Ca^{2+} fluxes into the postsynaptic cells. Previous reports suggest that oligomeric Aβ-induced Ca^{2+} influx occurs through postsynaptic NMDAR. Furthermore, this can lead to excessive formation of reactive oxygen species (ROS) and oxidative stress [4]. Synapses are formed by connections between two neurons that allow a neuronal cell to pass a signal to another cell. This channel usually gets damaged or lost in most neurodegenerative diseases (Fig. 2). Accumulating evidence

suggests that dysfunction and loss of synaptic connections may be an important early event underlying AD progression. Insightful synapse degeneration in AD is characterized by the worsening of cognitive function, synapse loss, and neuronal cell death [5]. Synaptic function and plasticity have also been extensively studied in the transgenic mouse models that show abnormal synaptic transmission and impaired long-term potentiation (LTP) which are often well associated with Aβ plaque formation [6]. Neurodegenerative disorders are characterized by progressive cell loss in specific neuronal populations and mechanisms that have been put forward to account for AD with aging including inflammation and oxidative stress [7, 8]. Recently, Rai et al. [9] also proved that NMDAR activation, excessive Ca^{2+} fluxes, and free radical generation are associated with synaptic dysfunction and tau phosphorylation [10]. Excessive amounts of glutamate are associated with intense transient influx of Ca^{2+}, leading to mitochondrial functional impairments characterized by activation of the permeability transition pores in the inner mitochondrial membrane, cytochrome c release and depletion of ATP, and simultaneous formation of ROS [11]. In addition, an increase in cytoplasmic Ca^{2+} triggers intracellular cascades which lead to increased levels of ROS and oxidative stress [12]. Analysis of AD brains revealed that the extensive synapse loss is strongly correlated with cognitive impairment [13]. Cognitive function in AD patients is also closely interrelated to the density of presynaptic glutamatergic neurons and postsynaptic neurotoxicity [8, 9, 14]. A previous report by Arendt [15] suggests that synaptic decline occurs early in disease progression and neuronal death alone is not sufficient for disease progression. Cooper and Bear [16] have reported that synapses are selectively removed prior to cell death and dementia in AD patient may therefore be attributed to progressive reduction in synaptic integrity [17]. Thus, proper synaptic function is crucial for learning and memory. Therefore, from previous observations, it seems that proper NMDAR and synapse function are necessary for learning and memory, and any improper in NMDAR and synapse function may lead to progression of AD pathogenesis. In this review, we connect the link between NMDAR-mediated oxidative stress, Ca^{2+} dysregulation, and kinases on synapse function.

NMDA Receptor-Mediated Oxidative Stress

NMDA type of glutamate receptor (NMDAR) plays an important role in learning and memory formation and also considered crucial for brain development and function in the central nervous system. Activation of NMDAR leads to cytosolic free intracellular Ca^{2+} increase [10] required for LTP and long-term depression (LTD) [18] and, more likely, for synaptic plasticity [19]. NMDA receptor subunit such as NR1, NR2A, and NR2B maintains the synaptic plasticity and neuronal function. The NR2A subunit is involved in the induction of LTP, whereas the NR2B subunit contributes to the formation of LTD and, thus, memory function. Elevation of cytosolic free Ca^{2+} leads to derangement of many intracellular processes that normally regulate Ca^{2+} sequestration and energy metabolism [7]. Modulations of Ca^{2+}, glutamate, and NMDAR also induce some other biochemical mechanisms such as oxidative stress which further compromise with cell death [8]. Oxidative stress is one of the most important mechanisms involved in toxic events observed in neuronal cells in different neurodegenerative disorders as measured by free radical generation and lipid peroxidation [20]. Under normal conditions, ROS act as signaling

molecules in many physiological processes including redox homeostasis and cellular signal transduction [21]. By activating proteins such as tyrosine kinases, mitogen-activated protein kinases and ROS are important mediators of signal transduction pathways [22]. Increased production of cellular ROS and oxidative stress has been reported to induce autophagy, a homeostatic process that enables cells to degrade cytoplasmic proteins and organelles [23]. Nitric oxide (NO) released by NO synthase may induce synaptic changes by causing neurotoxicity. Recent studies suggest that NO may be acting as a neuronal messenger in the central nervous system and is involved in the pathophysiology of neurodegenerative disorders [24]. Liu et al. [25] suggested that generation of reactive nitrogen species (RNS) and ROS triggers oxidative stress and eventually leads to neuronal damage. Thus, the increased free radical generation may ultimately lead to synaptic dysfunction which is an important pathophysiological component of AD [26]. Moreover, Kamat et al. [10] also suggest that oxidative stress causes cognitive deficiency, neurofibrillary tangle (NFT)-like pathological changes, and oxidative stress as seen in AD pathology via tau hyperphosphorylation. AD includes a variety of risk factors such as extracellular deposition of β-amyloid, accumulation of intracellular neurofibrillary tangles, oxidative neuronal damage, and inflammatory cascades [27]. Therefore, NMDAR activation, free radical generation, apoptosis, and their consequence on synapse function may lead to AD progression.

NMDA Receptor-Mediated Apoptotic Cell Death

Excitotoxic cell death (ECD) is a characteristic of mammalian brains in several types of neuronal apoptosis. A key event in ECD is a massive increase in intracellular Ca^{2+} by overstimulation of NMDAR. Excitotoxicity is defined as a toxic process characterized by a sustained stimulation of excitatory amino acid receptors mainly involving NMDARs [28, 29]. Different toxic events derived from excitotoxicity have been characterized in experimental models including upregulation of detrimental signaling pathways, disrupted Ca^{2+} homeostasis, and ROS/RNS with further oxidative/nitrosative stress ultimately leading to cell death [9]. Apoptosis plays a significant role in cell death during neurodegenerative disorders such as AD [30]. The activation of caspases, a major apoptotic pathway, is also characterized by mitochondrial dysfunction with the release of cytochrome c and activation of caspase-9 and, subsequently, of caspase-3 [7]. Lines of evidence suggest that caspase-3 activations were also found in the brain of AD patients [31]. Most neurons in the mammalian central nervous system possess receptors for apoptosis, the excitatory neurotransmitter glutamate. Overactivation of glutamate receptors can induce apoptosis by a mechanism involving Ca^{2+} influx [32]. Neuronal cell death is also triggered in response to increased oxidative stress, in which free radicals such as the superoxide anion radical and the hydroxyl radical damage cellular lipids, proteins, and nucleic acids [33]. So, collective information suggests that NMDAR-mediated oxidative stress and neuronal apoptosis directly or indirectly influences synapse function.

Biochemical Mechanism of Apoptosis and Synaptic Dysfunction

Biochemical mechanisms involved in apoptosis can be activated at synapse which can alter synaptic function and promote degeneration of synapses [34]. Apoptosis can be induced in

synaptosome preparations and neuritis of cultured brain neurons by insults that induce apoptosis in intact neurons. Caspase-mediated cleavage of synaptic proteins may control the process of neuronal apoptosis. α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunits are selectively degraded in hippocampal neurons after exposure to an apoptotic dose of glutamate, resulting in decreased Ca^{2+} influx and, thereby, preventing excitotoxicity [32]. Apoptotic pathways may also function in synaptic plasticity, particularly under conditions of stress and injury. The elevation of caspase-3 activity correlated temporally with memory impairment, reduced spine density and size, altered excitatory synaptic transmission, and enhanced LTD. Remarkably, pharmacologic inhibition of caspase-3 ameliorated the synaptic transmission, spine size, and memory deficits in these AD transgenic mice [35]. Increased caspase-3 activity is also reported in human AD brain, and elevated levels of caspase-3 are observed in the postsynaptic density fraction of AD brain [36]. Inhibition of caspase-3 activity is beneficial to reverse cognitive decline in APP mice possibly due to a requirement for caspase-3 activity in normal synaptic function [37, 38]. Thus, apoptotic executes by caspase-3 activation may contribute to neuronal apoptosis and synapse dysfunction and further provoke AD progression.

Mitochondria as a Regulator of Apoptosis and Oxidative Stress

Since most neurodegenerative disorders are associated with mitochondrial abnormalities, AD is associated with similar fashion of mitochondrial dysfunction. The mitochondria play a critical role in the regulation of apoptosis which is implicated in the aging process. Age-related mitochondrial oxidative stress may contribute to apoptosis [39]. The mitochondria are significantly reduced in various types of cells and its dysfunction is one of the causative pathophysiology of AD [40]. The most regular defect in mitochondrial electron transport enzymes in AD is a deficiency in cytochrome c oxidase which leads to an increase in ROS production, a reduction in energy stores, and disturbance in energy metabolism [41]. Indeed, ROS generation is an important mechanism accounting for cellular injury in many neurodegenerative disorders [42]. Such selective oxidative modification may cause the cells to be more vulnerable to apoptotic inducers [43]. Thus, the mitochondria appear to influence the aging process via modifying the regulatory machinery of apoptosis and that the mitochondria have a central role in aging-related neurodegenerative diseases like AD [7]. Consistently, oxidative stress-induced accumulation of Aβ-protein in AD causes lysosome membrane degradation and ultimately leads to neuronal cell death [44]. The mitochondria damaged by oxidative stress in pyramidal neurons of AD are subjected to neurodegeneration [45]. Thus, inhibition of the mitochondrial complexes leads to diminished ATP production and resulted in impaired energy metabolism. Several lines of evidence support that NO impairs mitochondrial/cellular respiration and other functions by inhibiting the activities of several key enzymes, particularly cytochrome c oxidase, and thereby causing ATP depletion [46]. In cultured neuroblastoma cells, overexpression of tau results in mitochondria with decreased ATP levels and increased susceptibility to oxidative stress [47]. Furthermore, the activity and composition of mitochondrial enzymes are disrupted in the mouse model of tauopathy [48]. Thus, tau may also directly influence mitochondrial function. It appears that mitochondria-mediated oxidative stress influences tau function, and the abnormal function

of tau also influences the mitochondria. Hence, the mitochondria and tau influence each other's function, which is profoundly associated with AD pathogenesis.

Molecular Mechanism of Oxidative Stress-Mediated Tau Phosphorylation

Inactivation of protein phosphatase 1/protein phosphatase 2A (PP1/PP2A) via oxidative stress has been shown in vitro and in vivo to be involved in hyperphosphorylation of tau and prolonged phosphorylation of extracellular receptor kinase (ERK) 1/2 [49]. Thus, it is intriguing to postulate that oxidative stress-mediated PP1 and PP2A inhibition in AD may account for enhanced ERK1/2 activity and subsequent tau hyperphosphorylation and neurofibrillary tangle formation. Li et al. [50] suggested that a decrease in PP2A activity causes the activation of ERK1/2, MEK1/2, and several other kinases and the abnormal hyperphosphorylation of tau both via an increase in its phosphorylation and a decrease in its dephosphorylation in AD brain. Stress-activated protein kinase (SAPK) and p38 MAPKs are members of the complex superfamily of MAP serine/threonine protein kinases. This superfamily also includes the ERKs (also referred to as MAPKs), which are typically activated by mitogens, c-Jun N-terminal kinase (JNK)/SAPK, and p38 mitogen-activated protein kinase (MAPK), which are known as stress-activated kinases [51]. This can be attributed to the fact that the activities of these enzymes are stimulated by a variety of exogenous and endogenous stress-inducing stimuli including ROS and oxidative stress (Fig. 3). The kinases that phosphorylate tau can be activated by NMDA-mediated oxidative stress such as hyperactivation of Cdk5 signaling pathway, MAPK, and several stress-activated protein kinases [52]. Thus, induction of this protein by JNK/SAPK could serve as a potential marker for pathologies associated with chronic oxidative stress. Among them, cyclic AMP-dependent protein kinase (PKA) and calcium-calmodulin-dependent protein kinase II (CaMKII) are associated with NMDAR remodeling. The phosphorylation of tau by these kinases inhibits the ability of tau to promote microtubule assembly and facilitates the polymerization of tau into paired helical filament (PHF) [53]. Protein phosphatase mediates the regulation of protein kinase C during long-term depression in the adult hippocampus in vivo. The neural substrates of learning and memory are thought to involve long-term changes in synaptic function, including LTD of synaptic strength. All these studies signify that inhibition of phosphates activates the number of kinases which actively participate in the activation of oxidative stress. Activation of kinases also stimulates the NMDAR and CaMKII remodeling. Moreover, inhibition of phosphatase also causes tau hyperphosphorylation, a critical event of AD pathology. Thus, phosphatase inhibition, kinase activation, NMDAR remodeling, and oxidative stress are strongly correlated with each other and, hence, influence synaptic function.

Modulation of NMDA Receptor and Kinases on Oxidative Stress

NMDA receptors influence death and survival pathways for synapse function. Activation of NMDAR induces the ERKs, which promote a signaling cascade important for neuronal survival. Thus, the synaptic NMDAR activates ERK, promoting cell survival [54], whereas the extra synaptic pool of NMDARs trigger mitochondrial membrane potential breakdown, as well as cell body and dendritic damage [55]. Moreover, activation of synaptic NMDAR leads to activation of the cAMP response element-binding protein (CREB), a transcription

factor also related to cell survival pathways [56, 57], and phosphorylates CREB [58]. Several studies have shown that oligomeric Aβ induces partial blockade of NMDAR currents, which leads to reduction of calcium influx that limits CaMKII function [59, 60]. In fact, oligomeric Aβ-mediated LTP impairment is believed to involve a decrease in the activation of MAPK, CaMKII, and Akt/protein kinase B, but not protein kinases A and C [61, 62]. Aβ has also been shown to induce synaptic depression by activating mGluRs, which triggers a series of downstream molecular events involving MAPK and calcineurin, which ultimately promotes internalization of AMPA receptors and synapse collapse [63]. Kinases that are important for synaptic function such as PKC, PKA, and CaMKII have reduced basal activity and stimulation-induced activation is impaired [64]. Phosphatase activity contributes to changes in phosphorylation state of bcl-2 family member protein BAD, and the CREB and dephosphorylation of BAD and CREB is associated with impaired memory [65]. This regulatory mechanism of Aβ influences NMDAR and CaMKII function and impairs learning and memory function. Abnormal function of Aβ also activates several stress-related kinases that cause oxidative stress and apoptosis, which are heavily implicated in AD pathogenesis (Fig. 4). In the later stage, all these disparities result into neuronal dysfunction and synaptic loss.

Glycogen Synthase Kinase-3β

Glycogen synthase kinase-3 (GSK-3) is a pivotal molecule in the development of AD. Inhibition of GSK-3 reduces the production of Aβ peptides in amyloid plaques and the hyperphosphorylation of tau protein in neurofibrillary tangles [66]. GSK-3beta is involved in the formation of PHF-tau, which is an integral component of the NFT deposits that disrupt neuronal function and a marker of neurodegeneration in AD [10, 67]. GSK-3 also phosphorylates and inhibits cAMP responsive element-binding protein [68], a universal modulator of memory and intermediate molecule of the NMDAR pathway. Moreover, GSK-3β promotes actin and tubulin assembly [69], processes required for synaptic reorganization during memory formation. Additionally, within the brain, MAPK inactivates GSK-3β by direct phosphorylation at its C-terminus [70]. Dephosphorylation of GSK-3 at inhibitory sites is coordinated by PP1, PP2A, and protein phosphatase 2B (PP2B, calcineurin) [71]. PP1 preferentially acts as a phosphatase for GSK-3β, while PP2A favors GSK-3α [72, 73]. On the other hand, the overexpression of GSK-3β inhibits PP2A, which may serve as a negative feedback mechanism for GSK-3β activity [74]. GSK-3β activity is negatively regulated by several signal transduction cascades that protect neurons against apoptosis suggesting the interesting possibility that activation of GSK-3β may contribute to neuronal apoptosis [75]. In response to oxidant stress, GSK-3β translocates to the mitochondria in a kinase activity-dependent manner and enhances production of cytotoxic ROS from mitochondria. This study identifies GSK-3β, a kinase known to participate in oxidative stress, cell death, and neurodegeneration, as a fundamental element in the downregulation of the antioxidant cell defense [76]. Collectively, it seems that Aβ activates GSK-3β which induces oxidative stress, hyperphosphorylation of tau, NFT formation, neuronal death, and synaptic loss that can induce memory deficits.

NMDA Receptor and Calcineurin (PP2B) Activity

Since intracellular Ca^{2+} coming from several sources and mostly through glutamate-mediated contribute to calcineurin (CaN) activation and may be preferentially increased by NMDAR activity in animals [77]. Furthermore, mild oxidative stress is thought to increase CaN activity through the release of Ca^{2+} from intracellular stores [78] or a decrease in effectiveness of inhibitory proteins [79]. This would suggest that the release of Ca^{2+} from intracellular stores could decrease NMDAR function through CaN activation and increased oxidative stress that can influence synapse function [80]. Chen et al. [81] have reported that β-amyloid reduces NMDAR function and impairs LTP through enhanced CaN activity. As the disease progression starts, increased expression of CaN inhibitory proteins may shift the balance of Ca^{2+}-activated kinases/phosphatases. Therefore, calcineurin alteration promotes tau phosphorylation, neurodegeneration, tangle formation [82, 83] and, subsequently, synapse dysfunction.

Phosphatase Inhibition, NMDA Receptor, Tau Hyperphosphorylation, and Synapse Function

Protein phosphatase inhibition leads to the induction of synaptic plasticity in the form of LTP involved in memory formation. Inhibition of protein phosphatases reduces postsynaptic signaling as a major mechanism for basal synaptic transmission and memory formation [84]. It has been reported that inhibition of protein phosphatases increases tau phosphorylation and initiates neuronal cell death which includes altered Ca^{2+} homeostasis and glutamate excitotoxicity that alter the memory formation [85, 86]. Previous reports suggested that accumulation and mislocalization of hyperphosphorylated tau in the somatodendritic compartment of neurons in AD disrupts glutamate receptor trafficking and synaptic function [87–89]. Not many available reports show how tau hyperphosphorylation and aggregation contributes to the synaptic deficits and neuronal death in AD. Hoover et al. [88] suggest that abnormal tau phosphorylation may also affect postsynaptic receptor targeting and display disrupted targeting of excitatory glutamate receptor and dendritic spines (Fig. 5). Impaired NMDAR can lead to dendritic spine dysfunction and removal of dendritic spine [90]. Tau protein also binds to a postsynaptic protein complex which includes PSD-95, the scaffold for synaptic NMDARs which is a critical regulator of synaptic plasticity [91]. Endogenous tau is typically present in dendrites in the postsynapse, where it interacts with the PSD-95/NMDAR complex [92]. Furthermore, microinjection of human tau into the presynaptic terminal of the squid axon has blocked synaptic transmission possibly by preventing proper docking of synaptic vesicles [93]. Therefore, tau may play an important role in regulating synaptic function and targeting neurotransmitter receptors to the synapse [94]. Zhang et al. [95, 96] also showed that glutamate release during stimulus and intracellular Ca^{2+} release from presynaptic terminals led to abnormal synapse function. These reports suggest that presynaptic dysfunction might be an early component of synaptic dysfunction in AD. Thus, lines of evidence supported that the tau protein is actively engaged in synapse dysfunction and associated with NMDAR function. In conclusion, the glutamate-induced excitotoxicity and synaptic dysfunction could be an excellent target for the therapy of AD.

NMDA Receptor and Synapse Function

NMDARs are located in neuronal cell membranes at synaptic and extrasynaptic locations, where they are believed to mediate distinct physiological and pathological processes. NMDARs are glutamate-gated ion channels that are highly permeable to Ca^{2+} and Ca^{2+} influx through NMDAR. This is essential for synaptogenesis. Synaptic remodeling leads to long-lasting changes in synaptic efficacy such as long-term potentiation and long-term depression [97]. The NMDARs are involved in cellular mechanism for learning and memory function [9]. NMDARs are involved in a wide array of biological processes which are crucial for brain development and function [98]. NMDAR activation might also play an important role in extracellular adenosine regulation, with important consequences for the regulation of excitatory synaptic transmission, plasticity, and excitotoxicity [99]. NMDAR activation also led to influx of Ca^{2+} through a ligand- and voltage-sensitive calcium channel [100], which triggered significant advances in understanding the cellular cascades initiated as a result of tetanic stimulation. The glutamatergic hypothesis of AD states that glutamate-related excitotoxic mechanisms involving the NMDAR lead to neurodegeneration and cell death [101]. The activation of glutamate receptors has also been found to induce the release of glutamate and induce a massive accumulation of Ca^{2+}. This influx of Ca^{2+} contributes to an alteration of cell function, leading to cell death either through free radicals or through overload of the mitochondria, resulting in free radical formation, caspase activation, and the release of apoptosis-inducing factors [7, 102]. Therefore, synaptic stimulation through NMDARs is important for learning and memory functions, but excess glutamate can over-stimulate these receptors resulting in excitotoxicity and neurodegeneration.

Glutamate and Aβ-Mediated Ca^{2+} Dysregulation and Synapse Function

Glutamate plays an essential role in learning and memory by triggering NMDAR to allow a controlled amount of calcium into a nerve cell. Ca^{2+} helps to create the chemical environment required for information storage. Excess glutamate, on the other hand, overstimulates NMDARs so that they allow even more calcium into nerve cells and the process leads to disruption and death of the cells [20]. It has been reported that inhibition of protein phosphatases increases tau phosphorylation and initiates neuronal cell death which include altered Ca^{2+} homeostasis and glutamate excitotoxicity [86]. In contrast to most disease models, aged animals exhibit neurologic changes that usually include synaptic dysfunction and Ca^{2+} dysregulation [103]. Aβ plaques, a pathological feature of AD, induce extracellular accumulation of glutamate and intracellular deposition of calcium ion Ca^{2+}. In vivo Ca^{2+} imaging studies corroborate the idea that different subsets of neurons in AD transgenic mice can be found exclusively near Aβ plaques and appeared to result from a relative decrease in synaptic inhibition [104]. In vivo imaging of aged APP transgenic mouse brain shows elevated intracellular Ca^{2+} and aberrant Ca^{2+} homeostasis in a subset of neurites in close proximity of Aβ plaques [105]. The abnormal Ca^{2+} handling of neurons affected by Aβ is associated with loss of dendritic spines and neuritic dystrophy, mediated in part by the Ca^{2+}-dependent protein phosphatase calcineurin [106]. It is notable that calcineurin is also required for apoptosis and LTD, as well as for Aβ-induced spine loss and endocytosis of NMDARs [107]. Thus, a large buildup of glutamate can occur and induce a

massive accumulation of Ca^{2+}, leading to apoptosis. It has also been noted that Aβ plaques increase neurons' vulnerability to excitotoxicity and loss of synaptic protein.

NMDA Receptor, CaMKII, and CREB

The transcription factor CREB plays an essential role in the maintenance of LTP. CREB signaling has been recently involved in several brain pathological conditions including cognitive and neurodegenerative disorders. Altered hippocampal-dependent synaptic plasticity and memory mediates synapse loss through the CREB signaling pathway [108]. The activation of CREB by phosphorylation is triggered in neurons by a wide variety of signaling processes, from increases in intracellular Ca^{2+} through activation of voltage- or ligand-gated channels to changes in cAMP levels. The phosphorylation of CREB by kinases from several signaling pathways may be a mechanism for memory formation [109]. Activation of synaptic NMDARs toward CaMKII, which may also phosphorylate and activate CREB in neurons, is associated with increased Ca^{2+} [110]. Interestingly, the increase in nuclear Ca^{2+} can also activate CREB, indicating that nuclear kinases may have a direct role in the modulation of CREB activity [111]. Loss of excitatory synapses in the hippocampus induced by Aβ requires functional NMDARs for proper synapse maintenance [61]. Aβ also influences CREB activation, which is crucial for the maintenance of LTP. LTP plays a crucial role in memory formation. Vitolo et al. [112] showed that Aβ decreases the activity of CREB and thus reduces the expression of genes encoding proteins that are essential for LTP. Another study found that excessive activation of extrasynaptic NR2B-containing NMDARs, which leads to downregulation of CREB, underlies oligomeric Aβ-mediated LTP inhibition [113]. Thus, it may be inferred from the above reports that Aβ also modulates CaMKII, CREB, and NMDAR essential for maintenance of LTP.

Therapeutic Strategies

The therapies applied till date for the treatment of AD include the following: antibody vaccination and immunization therapies; gene therapy; enzyme-based therapies such as β-secretase inhibitors, -secretase inhibitors and modulators, and cholinesterase inhibitors; receptor-based therapies such as NMDA receptor antagonists, AMPA receptor modulators, peroxisome proliferator-activated receptor agonists, M1 muscarinic agonists, receptor for advanced glycation end product-related mechanisms, ad nicotine acetylcholine receptor agonists; redox stress-based therapies such as antioxidants and anti-inflammatory and neuroprotective approaches; and tau-related therapies. Moreover, several other therapies were also designed to treat AD by targeting cholesterol biosynthesis, astrocyte-modulating agents, homocysteine-lowering strategies, and caspase inhibitors. Most of the abovementioned therapies also passed through clinical trials but results were not successful so far. Among all the therapies which are currently in the market, only two classes of drugs are available for commercial purpose such as the cholinesterase inhibitor and NMDA receptor antagonist. However, these classes of drugs are also not successful either to give complete remedy from AD. There may be some significant gaps which are necessary to understand and improve the current therapies.

Significant Gap in Research

Oxidative stress-induced damage in the brain is associated with aging and is usually involved in the development of AD pathology in a clinical set of condition. Some observational studies have suggested that antioxidant therapy could overcome the disease progression of AD. Much research has been carried out with antioxidant therapy, but antioxidant randomized clinical trials in AD have had mixed results. Oxidative stress is a well-established pathophysiological factor in AD but till now the use of antioxidants in the prevention or therapy gave conflicting results. Some of the reports have shown antioxidant therapy for the betterment of AD pathology (Table 1), but still therapy is not so promising. In our opinion, antioxidant therapy alone is not looking so hopeful. We should use some more specific targets with combinational therapy rather than a single antioxidant such as NMDAR antagonist, neuronal kinases, and antioxidant as well as flavonoids.

Future Direction

In conclusion, through this review, we have tried to give our perspective on the wide variety of interaction between NMDAR-mediated oxidative stresses with the etiology of Alzheimer's disease. NMDAR-mediated oxidative stress mechanisms are likely to play an important role in the synapse dysfunction in the pathogenesis of AD. Moreover, mitochondrial-mediated oxidative stress and apoptosis are also suggested to be contributing factors in AD pathogenesis. Furthermore, oxidative stress-mediated kinase and tau phosphorylation provides a connection of synapse dysfunction in AD. As we are not getting complete remedies from antioxidant therapy or known NMDAR antagonist drug used for AD pathology, should we go for combinational therapy? Or are there so many intermediate molecules between NMDAR to neurodegeneration? Should we go for target intermediate molecules? Therefore, understanding the role of oxidative stress-associated molecule and kinases in synapse dysfunction during AD pathogenesis may also lead to the development of mechanism-based therapeutics and better constructive strategies.

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Abbreviations

AD	Alzheimer's disease
CNS	Central nervous system
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
NMDA receptor	*N*-methyl-D-aspartate receptor
Aβ	Beta amyloid
APP	Amyloid precursor protein

CaMKII	Calmodulin-dependent protein kinase
NFT	Neurofibrillary tangle
NO	Nitric oxide
PP	Protein phosphatase
MAPK	Mitogen-activated protein kinase
PKA	Protein kinase
ERK	Extracellular receptor kinase
ECD	Excitotoxic cell death
LTD	Depression
LTP	Long-term potentiation
CREB	cAMP response element-binding protein
GSK-3β	Glycogen synthase-3β

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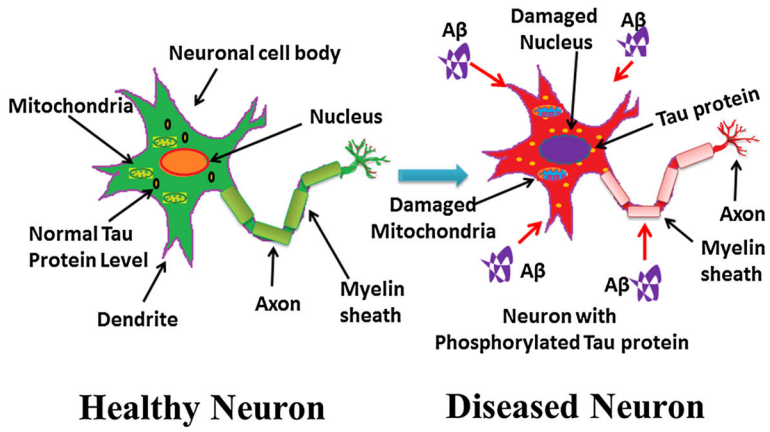

Fig. 1.

Comparative changes in healthy and diseased neuron implicated in AD pathogenesis. The abnormal function of Aβ activates several stress-related kinases that results in damaged nucleus and mitochondria in diseased neurons in AD pathogenesis

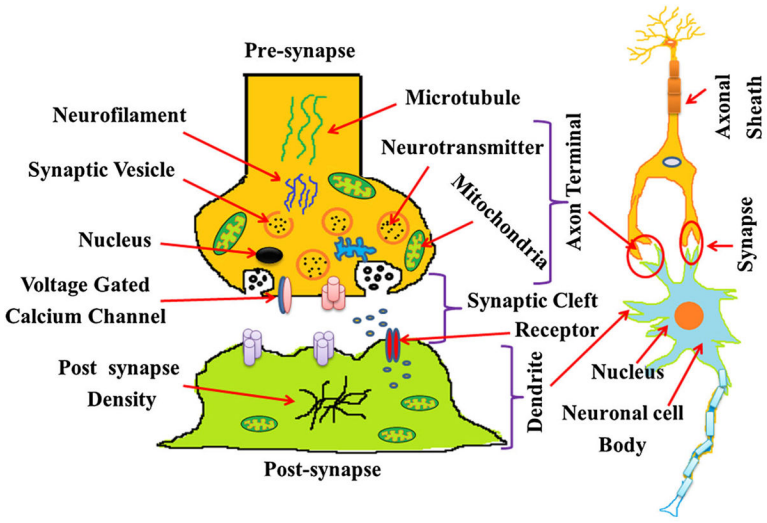

Fig. 2.

Structure of synapse: Synapse is a specialized communication junction between two cells comprised of two major units: a presynaptic cell (usually a neuron) that sends out a signal and a postsynaptic cell that receives the signal. Neurotransmitter molecules diffuse across the synaptic cleft and bind to their specific receptors on the postsynaptic cell. This recreates the action potential in the postsynaptic cell. This channel usually gets damaged or lost in neurodegenerative diseases

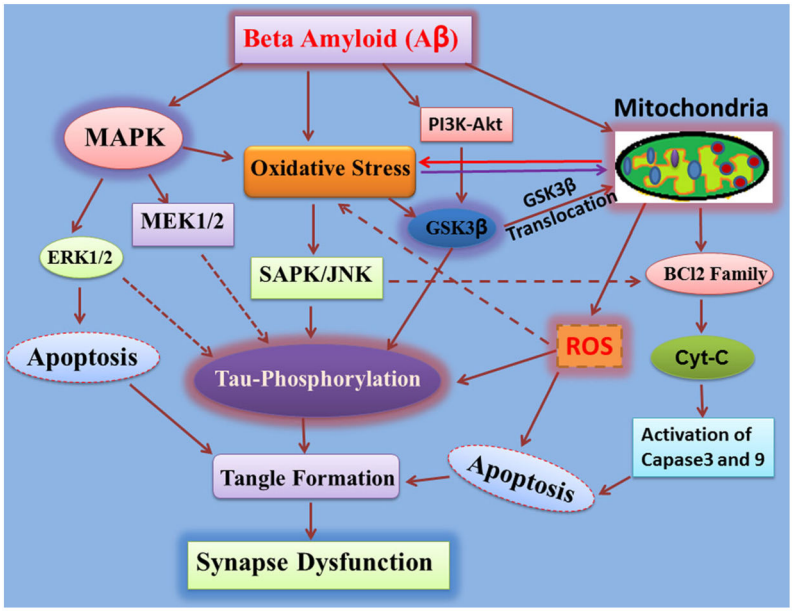

Fig. 3.

Synapse dysfunction: as a consequence of MAPK and mitochondrial oxidative stress-mediated tau hyperphosphorylation. β-Amyloid activates several stress-related kinases that causes oxidative stress. The phosphorylation/activation of ERK1/2 and MEK1/2 via MAPK results in apoptosis. Consequently, abnormal hyperphosphorylation of tau leads to synapse dysfunction. Aβ also results in mitochondrial dysfunction by affecting the prosurvival protein Bcl-2. The mitochondrial-mediated caspase pathway gets triggered by the Bcl-2 family of proteins, then cytochrome c release, and finally, apoptosis. This ultimately leads to synapse dysfunction

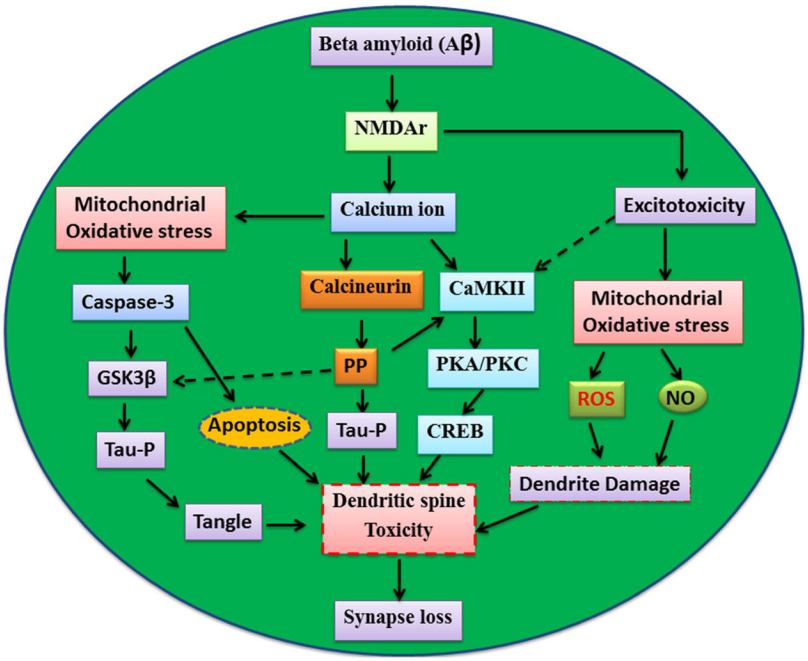

Fig. 4.

Molecular mechanism of tau phosphorylation mediated synaptic dysfunction: High level of Aβ production is directly correlated with critical event for synaptic dysfunction, i.e., formation of tangles. Excitotoxic cell death (ECD) is an event due to increased intracellular Ca^{2+} by overstimulation of NMDA receptor. Overstimulation of NMDAR leads to upregulation of detrimental signaling pathways, disrupting Ca^{2+} homeostasis and oxidative/nitrosative stress ultimately toward apoptosis. The mitochondrial oxidative stress and the release of cytochrome c, activation of caspase-9, and subsequently of caspase-3 cause neuronal damage. Mitochondria-mediated oxidative stress influences tau function resulting in the hyperphosphorylation of tau which governs the major synaptic dysfunction by forming tangles

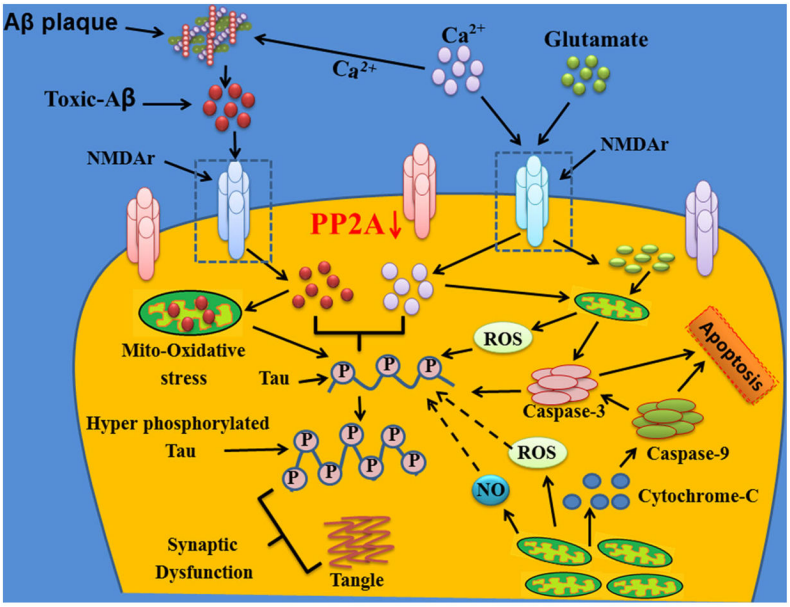

Fig. 5.

Beta amyloid-mediated synapse loss: Deposition of amyloid plaques (Aβ) is characterized in Alzheimer's disease (AD) which affects NMDAR resulting in dendritic damage caused due to mitochondrial oxidative stress as a consequence of excitotoxicity. Aβ also trigger NMDA mediated Ca^{2+} influx which results in dendritic spine toxicity mediated by CREB and hyperphosphorylation of Tau. Ca^{2+} influx can also lead to mitochondrial oxidative stress along with caspase-3-mediated apoptosis and tau hyperphosphorylation and ultimately leads to synapse loss

Table 1

List of pharmacologically active antioxidants, flavonoids, and vitamins used in AD pathology

S. nos.	Antioxidants/flavanoids	References
1	Vitamin C and vitamin E	[114, 115]
2	Vitamin C	[116]
3	Vitamin B_{12}	[117, 118]
4	Vitamin E	[119–123]
5	α-Lipoic acid, CoQ10	[124, 125]
6	Selenium and vitamin E	[126]
7	MnSOD	[127]
8	Curcumin	[128, 129]
9	Memory XL (folic acid, vitamin B_{12}, vitamin E, acetyl-L-carnitine, SAM, NAC)	[130, 131]
10	Ebenone/idebenone	[132–134]
11	Estrogen	[135, 136]
12	Colostrinin	[137–140]
13	Epigallocatechine gallate (EGCG)	[141]
14	Resveratrol	[142, 143]
15	Pramipexole	[144]
16	Latrepirdine	[145, 146]
17	Ubiquinone, vitamin E, or lipoic acid	[147, 148]
18	Lipoic acid	[149]
19	Silibinin/quercitin	[150–152]
19	Melatonin	[153–155]
20	Caffeine	[156]
21	Selegiline (L-deprenyl)	[119]
22	*Ginkgo biloba*	[157–159]
23	Gugulipid	[160, 161]