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Amyloid Beta as a Modulator of Synaptic Plasticity

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Abstract

Alzheimer's disease is associated with synapse loss, memory dysfunction and pathological accumulation of amyloid beta in plaques. However, an exclusively pathological role for amyloid beta is being challenged by new evidence for an essential function of amyloid beta at the synapse. Amyloid beta protein exists in different assembly states in the central nervous system and plays distinct roles ranging from synapse and memory formation to memory loss and neuronal cell death. Amyloid beta is present in the brain of symptom-free people where it likely performs important physiological roles. New evidence indicates that synaptic activity directly evokes the release of amyloid beta at the synapse. At physiological levels, amyloid beta is a normal, soluble product of neuronal metabolism that regulates synaptic function beginning early in life. Monomeric amyloid beta 40 and 42 are the predominant forms required for synaptic plasticity and neuronal survival. With age, some assemblies of amyloid beta are associated with synaptic failure and Alzheimer's disease pathology, possibly targeting the N-methyl-D-aspartic acid (NMDA) receptor through the α7-nicotinic acetylcholine receptor (α7-nAChR), mitochondrial amyloid-β alcohol dehydrogenase (ABAD) and cyclophilin D. But emerging data suggests a distinction between age effects on the target response in contrast to the assembly state or the accumulation of the peptide. Both aging and beta amyloid independently decrease neuronal plasticity. Our laboratory has reported that amyloid beta, glutamate and lactic acid are each increasingly toxic with neuron age. The basis of the age-related toxicity partly resides in age-related mitochondrial dysfunction and an oxidative shift in mitochondrial and cytoplasmic redox potential. In turn, signaling through phosphorylated extracellular signal-regulated protein kinases (pERK) is affected along with an age-independent increase in phosphorylated cAMP response element-binding protein (pCREB) This review examines the long-awaited functional impact of amyloid beta on synaptic plasticity.

Keywords

Alzheimer's disease; Synapse; Aging; mitochondria; survival signaling

1. Introduction

Alzheimer's disease (AD) arises on a neuropathological background of amyloid plaques and neurofibrillary tangles (NFT) characterized by ongoing neurodegeneration in areas of brain involved in learning and memory. Synaptic pathology is an early marker of both AD and aging [1,2,3]. The best understood AD pathogenesis could be explained by a loss of plasticity [4,5] that may adversely affect dendritic ramifications, synaptic remodeling, long-

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term potentiation (LTP), axonal sprouting, neurite extension, synaptogenesis, and neurogenesis. Plasticity, the process by which synapses modulate their strength and form new connections with other neurons plays a particularly important role in response to injury and disease [6]. Age is the most important and universal risk factor for AD perhaps because the biological capacity for plasticity decreases with age [7,8]. With aging, a combination of subclinical AD pathology, inflammation, Lewy bodies, microinfarcts and vascular lesions in the cortical and hippocampal regions contribute to late-life brain atrophy and dementia in each individual [9]. Thus, as a consequence of age, the ability to sustain learning and memory are diminished or slowed [10]. Age could interact with other variables that influence neuroplasticity in at least two ways. Conventionally, aging may shift the complex balance of amyloid beta (Aβ) metabolism away from the potentially neurotrophic products of α secretase processing and toward the production of neurotoxic moieties containing the intact Aβ fragment [11]. Alternatively, aging could render the brain vulnerable to Aβ-protein neurotoxicity [12] an age-related susceptibility [13]. Aβ toxicity in vivo is also highly species-specific; toxicity is greater in aged rhesus monkeys than in aged marmoset monkeys, and is not significant in aged rats [12]. These results suggest that Aβ neurotoxicity in vivo is a pathological response of the aging brain, which is more pronounced in higher order primates. Thus, longevity may contribute to the unique susceptibility of humans to AD by rendering the brain vulnerable to Aβ neurotoxicity [12]. The pathological hallmark of Aβ deposits appears to precede the hallmark of phosphorylated tau in the brain [14]. Aβ1-42 at high doses impairs cognitive and memory functions in mouse models of AD. But the relationship of Aβ deposition to synapse loss is less clear in these models. Additionally, whether Aβ deposits might be the early symptom contributing to neurodegeneration or whether synaptic pathology might be an early event preceding amyloid deposition in AD is not clear. Synaptic loss might occur early in AD and molecular biomarkers such as tau hyperphosphorylation and Aβ deposits might be indicators of prolonged disease. Moreover, a central question is whether Aβ plays a direct role in the neurodegenerative process in AD. There are two schools of thought on involvement of Aβ in Alzheimer's disease. In one, Aβ initiates the disease once produced in excess, which has motivated most AD clinical trials. Alternatively, Aβ does not initiate but rather is secondary to other pathogenic events as a protective response to neuronal insult [15].

Two models have emerged to explain the role of Aβ in normal and AD pathological state. According to the most popular model, oligomeric [16] and fibrillary Aβ deposits [17,18] are responsible for the eventual neuronal degeneration involving disruption of glutamatergic synaptic function leading to the characteristic cognitive deficits [19,20,21,22]. The second model dictates that Aβ may normally serve as a negative feedback signal that maintains neuronal activity within a normal dynamic range. *In vivo* studies on wild-type animals [23] and *in vitro* studies on wild-type [24] and knock-out [25] animals demonstrate that Aβ production significantly increases with increase in communication between brain cells [26] and this increased level depresses excitatory synapses and reduces neuronal activity. Aβ was proposed as a regulator of ion channel function [27] and as essential for neuronal health [28]. Aβ is secreted from neurons in response to synaptic activity and that Aβ, in turn, down regulates synaptic transmission [29]. This negative feedback loop could operate as a physiological homeostatic mechanism to limit levels of neuronal activity [30].

A youthful role for Aβ may enhance neuronal plasticity to help the remaining neural circuits compensate for lost or broken circuits and improve overall network performance and neurological function (Figure 1). Improving network activity may also help to prevent the inexorable loss of neuronal processes and cell bodies that occurs in AD and other neurodegenerative disorders. In the present paper we discuss the recent mechanistic link between Aβ function and synaptic plasticity. This review focuses on the interface between a

physiological role of Aβ and toxicity in terms of molecular mechanisms of synaptic plasticity.

2. Aβ formation and assembly

The Aβ peptide is derived by proteolytic processing of the amyloid precursor protein [APP; 31,32], a type I integral membrane protein [33]. Aβ is a prominent constituent of the amyloid plaques present in AD brain [34]. In the beginning, APP is delivered to the plasma membrane where it is subjected to proteolytic processing by α-secretase. However, absent the α-secretase cleavage, APP molecules are internalized into endocytic compartments where they are subjected to cleavage by β-secretase (BACE) and γ-secretase to generate Aβ. Therefore, inhibition of the combined action of β- and γ-secretase that leads to Aβ peptide generation is regarded as a promising approach to treat AD. The Golgi apparatus and to a lesser extent the endoplasmic reticulum are also sources of a distinct population of Aβ peptides secreted into the extracellular space [35]. The majority of secreted Aβ peptides are 40 amino acids in length (Aβ40), whereas a smaller fraction of Aβ is cleaved to produce a 42 amino acid species (Aβ42). Aβ42 is the main amyloid peptide that drives production of amyloid fibrils [36] in AD patients. Aβ in turn can be degraded by proteases such as the insulin-degrading enzyme [37,38] and neprilysin [39]. Aβ generated from axon-transported APP is released from presynaptic sites and subsequently accumulates close to the nerve terminal [40].

The hydrophobicity of Aβ42 leads to a number of aggregation states [41]. This ability to self-associate [49,50] into different assembly states ranges from dimers to soluble oligomers to insoluble aggregates of fibrils [51]. Initially, it was assumed that toxicity was mediated by fibrillar Aβ similar to that present in amyloid plaques. This together with the findings that monomer is innocuous and that amyloid plaques alone cannot account for disease has lead many to conclude, if it isn't fibrillar Aβ and it isn't Aβ monomer then it must be some other form of Aβ [52]. Soluble non-fibrillar Aβ assemblies [19,53] are more toxic than the fibrillar form, but as yet the specific form of Aβ which causes injury to neurons *in vivo* has not been identified. These oligomers have been described in cultured cells [44] as well as in APP transgenic mouse brain and human brain [45,46,47,48]. Synthetic oligomers specifically bind to synapses of hippocampal neurons [42,43]. Soluble Aβ (sAβ) is found, at low concentrations, as a normal constituent of biological fluids [54,55,56]. As demonstrated by Piccini et al. [57], the composition as well as the aggregation and toxicity properties of soluble Aβ aggregates that accumulate in AD is different from those of normal aging. One such form of Aβ known as N-terminal truncated pyroglutamyl amyloid peptide (Aβpy3-42) is the predominant form of early aggregates that alter the membrane permeability, suggesting that they form pores in the membrane like other amyloidogenic peptides [57,58]. Naturally occurring Aβ peptides can begin to assemble in vivo into metastable dimers, trimers and higher oligomers while still at low nanomolar levels [44,59,60]. Immunocytochemical approaches identified different forms of Aβ produced with age in an APP transgenic (Tg2576) mouse model of AD [61]. Initially Aβ40 and Aβ42, the most predominant form of Aβ, occurs in its soluble form. At 6–10 months, the soluble forms of Aβ decrease as SDS-insoluble forms of Aβ40 and Aβ42 increase exponentially. SDS-resistant Aβoligomers develop only in older Tg2576. After 11–12 months, Aβ is converted into diffuse plaques. At later ages, the Aβ accumulates in diffuse plaques, neuritic plaques with amyloid cores [61]. It seems reasonable that the synaptic and neuronal compromise seen at sites distant from plaques is mediated by an Aβ species that can readily diffuse and access the space in and surrounding the synaptic cleft [52]. The physiological level of Aβ is controlled by its production, degradation and clearance [23,62] while a defect in clearance leads to the accumulation of Aβ [52].

3. Activity-dependent Aβ production

Since synaptic loss correlates better with memory loss than plaque burden and people with mutations in the APP gene who make more amyloid invariably develop AD, the critical question emerges, what is the role of Aβ in synaptic activity and progression of the disease process? The mechanism regulating Aβ production and its subsequent release by neurons is closely linked with synaptic activity [29]. Thus, understanding the factors that regulate Aβ levels has implications for disease pathogenesis as well as for developing therapeutics. In animal models as well as in humans, the activation of muscarinic M1 acetylcholine receptors increases α-secretase cleavage of APP and consequently reduces Aβ levels [63,64] whereas activation of NMDARs decreases α-secretase cleavage, consequently increasing Aβ levels [65]. Stimulation with muscarinic agonists or activators of protein kinase C (PKC), such as phorbol esters causes the up-regulation of the α-secretase cleavage of APP [66]. Thus, regulation of the α-secretase contributes to regulation of Aβ peptide and toxicity in vivo [67]. Modulating synaptic transmission has been shown to alter extracellular soluble Aβ levels in organotypic brain slice [29]. Synaptic activity modulates interstitial fluid Aβ levels in vivo in APP transgenic and wild-type mice [23]. Neural activity regulates the trafficking of proteins at synaptic sites [68,69]. Thus it is possible that the induction of neural activity promotes the endocytosis of surface APP, enhancing the accessibility of APP to BACE in endosomal/recycling compartments [29]. In acute brain slices, synaptic vesicle cycling alone, in the absence of neuronal depolarization, was sufficient to drive release of Aβ from neurons [23]. Similar increases in Aβ levels were demonstrated in hippocampal seizures induced by electrical stimulation. However, decreasing synaptic transmission using tetrodotoxin (TTX) or tetanus toxin rapidly reduced interstitial fluid Aβ levels by 30% and 80%, respectively [26]. Cirrito et al. [26] also show that synaptic activity-induced increase in endocytosis drives more APP into the endocytic compartment, ultimately resulting in increased Aβ production and release. Aβ produced in the endocytic pathway is then brought to the cell surface where it is released into the extracellular fluid [70]. Inhibition of endocytosis reduces APP internalization and reduces Aβ production and release in cell lines [71]. Support for a casual link between synaptic activity and Aβ levels in humans comes from recent brain imaging studies of regions that contain the most metabolic activity throughout life (and presumably have the highest levels of neuronal activity) are the same regions that degenerate and accumulate Aβ [72]. The increased synaptic activity enhances both oligomer formation and localization at synaptic sites in rat and mouse hippocampal slices and primary human cortical neurons in culture [73]. These oligomers appear to bind to NMDARs at the synapse [74] and induce internalization of NMDAR [75] and deregulation of NMDA signaling pathways [76]. In this regard, neuronal activity not only enhances oligomer targeting but also facilitates oligomer formation at synaptic sites [73]. These findings indicate that sustained synaptic activity causes an increase in oligomeric Aβ which accumulates with age and leads to synaptic dysfunction and neuronal death. There seems to be a homeostasis of a normal negative feedback function under normal physiological conditions where an increased neuronal activity produces more Aβ; the enhanced Aβ production depresses synaptic function; the depressed synaptic function will decrease neuronal activity [29]. Disturbances in this homeostatic mechanism of Aβ could produce the problems of AD patients. Persistently elevated neuronal activity if it is unchecked could lead to excitotoxicity [77], as well as higher levels of secreted Aβ peptides, which may convert to neurotoxic fibrils with consequent synaptic depression and neuronal toxicity [78,79]. Thus Aβ toxicity might represent a disturbance of normal function with the net balance of production *versus* clearance determining a beneficial synaptic or toxic fate.

4. A normal physiologic role for Aβ

Aβ has been extensively studied because of its association with plaques in AD brains, interference with synaptic functionand possible pathogenesis of AD [60]. However, Aβ exists in normal individuals without any known pathology. Therefore, there has been a conscientious search for its normal physiological role in the brain, particularly its possible involvement in synaptic plasticity and neuronal survival. Aβ at physiological levels is essential for synaptic plasticity in normal individuals [80]. The physiological functions of Aβ, as well as the primary mechanisms that initiate early Aβ-mediated synaptic plasticity are now being revealed. We hypothesize that the protective or destructive effects of Aβ are determined by its relative concentration in addition to the age-related cellular environment. Physiologically low regulated concentrations of Aβ would play a critical function in mediating synaptic plasticity and improve cognitive functions whereas, accumulation of higher concentrations of Aβ together with age effects cause disruptions of this regulation with consequent synaptic dysfunction and loss, as seen in AD [76]. Other factors such as structural changes of Aβ due to pathological processing and/or post-translational dysregulations as well as age related changes in Aβ clearance cannot be excluded. The large body of evidence for activity-dependent production of Aβ strongly suggests a normal function for this peptide. Proposed functions of Aβ include control of synaptic activity and memory consolidation, trophic and neuronal survival, cholesterol transport and antioxidant functions.

4.1. Lower levels of Aβ modulate synapticplasticity

It is generally believed that plasticity, such as LTP and long-term depression (LTD), is important for learning and memory. Multiple signaling pathways, including several protein kinases and phosphatases, are required for the generation of LTP and LTD [81]. These same pathways have been shown to influence *in vivo* phenomena, such as learning and memory [82]. Aβ is released in lower amounts in normal brains throughout life during synaptic activity and seems to be beneficial for normal brain synaptic functions [83]. Aβ is normally produced in the brain, where the *in vivo* concentration in the rodent brain has been estimated to be in the picomolar range [84]. Picomolar Aβ is present in both cerebrospinal fluid and plasma of healthy individuals throughout life [55]. Recent results indicate that Aβ serves an essential role at the synapse and in synaptic structure-functional plasticity critical to learning and memory. A necessary role of Aβ in synaptic plasticity and memory in normal brain is supported by the observation that APP knock-out (KO) mice show impaired LTP and memory [85]. The impaired synaptic plasticity and memory found in BACE1 KO mice also suggest a necessary role of Aβ [86]. Similarly, the necessary role of Aβ in synaptic plasticity and memory is seen from loss of presenillin function (γ-secretase) [87]. Puzzo et al. [83] show thatpicomolar concentrations (200 pM) of both Aβ42 monomers and oligomers cause a marked increase in long-term potentiation, whereas high nanomolar concentrations (200 nanomolar) lead to the well established reduction of potentiation in the hippocampus. Picomolar levels of Aβ42 also produce a pronounced enhancement of both reference and contextual fear memory. Thus, lower concentrations play a novel positive modulatory role on neurotransmission and memory, whereas high concentrations are associated with neuronal cell death. The lower concentrations of aged Aβ42used by Puzzo et al.[83] are close to those found in the normal brain [88,89,90,91] and shown to enhance LTP and memory. Increase in synaptic activity will increase Aβ production [29] while lowering synaptic activity minimizes Aβ production. Similarly specific stimulation of NMDA receptors promotes Aβ production [65] and Aβ in turn depresses synaptic activity. Thus indirectly Aβ also plays a role in suppressing excessive glutamate release. Interestingly, Aβ may play an important role during synapse elimination [92] and stimulatation of neurogenesis in the hippocampus during brain development [93]. These studies provide

convincing evidence to show that physiological levels of Aβ have a role in controlling synaptic activity.

4.2. Neuronal survival

Aβ42 is normally produced and secreted by cells in much lower quantities than Aβ40, which represents ~90% of the total secreted Aβ [94]. However both species of Aβ are necessary for neuronal survival. Both Aβ40 and Aβ42 at physiological concentrations are important in neuronal survival and memory (Table 1). Physiological levels of Aβ also have trophic and neuroprotective actions in trophic deprived conditions [95]. Many Aβ has a physiological role in normal synapse function. In organotypic hippocampal slices, BACE activity is increased by synaptic activity and the resulting Aβ peptides depress excitatory transmission through α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and N-methyl-D-aspartic acid (NMDA) receptors, suggesting a role for Aβ in homeostatic plasticity [29]. Aβ may have an important physiological role in synapse elimination during brain development [reviewed in reference 92]. Inhibition of endogenous Aβ production by exposure to inhibitors either of β- or γ-secretases in primary neuronal cultures caused neuronal cell death [28]. Thus targeting Aβ formation pharmacologically, or immunologically, could be deleterious [96]. Both Aβ40 and Aβ42 have been shown to be protective. Synthetic Aβ42 monomers at 30–100 nM support the survival of developing neurons under conditions of trophic deprivation and protect mature neurons against excitotoxic death [97]. In cultured neural stem cells, Aβ42 increased the number of newborn neurons [93]. Aβ42 exhibited highly protective effects not only when combined with NMDA (100 nM), but also when applied before or after the NMDA pulse [97]. The later evidence excludes a direct interaction between Aβ42 monomers and NMDARs. Monomers of Aβ40 were also fully protective against NMDA toxicity. Neurotrophic function of Aβ40 was obtained in a cell culture treated with picomolar levels of Aβ40 [98,28]. Cells treated with such picomolar levels of Aβ40 reverse the toxicity of secretase inhibition. These findings provide compelling evidence for a role for Aβ in neuronal survival. The pro-survival role of Aβ is summarized in Fig. 1.

4.2.1. Insulin like growth factor-I (IGF-I) and insulin signaling—The underlying mechanism of neuronal survival with Aβ is emerging. Neuronal synapses and astrocytes of memory-processing brain regions possess insulin receptors (IRs) [99] which when activated by insulin facilitate synaptic plasticity in normal brain [100]. IR and Insulin-like growth factor I (IGF-I) receptors consist of α-subunits and transmembrane β-subunits. Binding of insulin or IGF-I to the α-subunit increases the intrinsic tyrosine kinase activity of the β-subunit, and causes autophosphorylation of the β-subunit, thus triggering tyrosine phosphorylation of insulin receptor substrate (IRS)-1 and IRS-2, as well as Shc [101] as an important pathway of cell survival. To protect against Aβ toxicity, the tyrosine-phosphorylated sites create binding sites for various signal-transducing molecules containing Src homology-2 domain, such as phosphoinositide 3-kinase (PI3K) and growth factor receptor-bound protein 2 (Grb2), thus activating PI3K/phosphoinostide-dependent kinase 1 (PDK1)/Akt (protein kinase B)/glycogen synthase kinase (GSK)-3α/-3β and Ras/Raf-1/mitogen-activated protein kinase/extracellular-signal regulated kinase (MEK/ERK) signaling pathways [101]. In normal brain, IGF-I and insulin promote glucose utilization, energy metabolism, and neuronal survival [102], largely through PI3K/Akt/GSK-3β signaling [103,104]. Consistent with positive effects of insulin on synaptic plasticity [105], acute insulin treatment improved memory in rats [106] and also in normaladults and AD patients [107] by strongly activating ERK and Akt and blocking c-Jun N-terminal kinase (JNK) activation in a PI3K-dependent manner [108]. The mechanism involves many steps beginning with Aβ activation of IGF-1/insulin receptors by locally produced IGF-1 or,

possibly, Aβ monomers may bind to IGF-1/insulin receptors, as already shown for Aβ oligomers [109,110].

4.2.2. The PI3K/Akt signaling—PI3K, a membrane-associated second messenger protein, and its downstream kinase, Akt, are associated with neuronal survival [111] and plasticity [112] via activation of transcription pathways and protein synthesis. PI3K pathway, which required the activation of IGF-1/insulin receptors, is the most convincing prosurvival effect of Aβ42 monomers. The PI3K signaling pathway is important in the transmission of survival signals in many cell types including neurons [113,114]. The PI3K-Akt signaling cascade, initiated by IRS, is phosphorylated by stimulated insulin- andIGF-receptor tyrosine kinases [115]. One of the kinases known to lie downstream of PI3K is Akt, which can be directly activated by products of PI3K [116] by promoting its phosphorylation at Ser473 and Thr308 [117]. Activated Akt, in turn, phosphorylates a wide range of substrates activating anti-apoptotic (survival) factors and inactivating pro-apoptotic factors [114,117]. Certain proapoptotic mediators, such as the transcription factor forkhead (FOXO), the tau kinase GSK-3β, and the Bcl2 antagonist BAD proteins, are inactivated by Akt [118,119]. Akt substrates such as mammalian target of rapamycin (mTOR; Ser2448) and decreased levels of cell-cycle inhibitors ($p27^{kip1}$) are found in AD temporal cortex when compared to controls [120]. Akt downregulates the activities of GSK-3α and GSK-3β by phosphorylating the former at Ser21 and the latter at Ser9 [118]. GSK-3α has been implicated in the production of Aβ peptide [117,121] while increased GSK-3β activity has been implicated in tau hyperphosphorylation [122,123,124] and neuronal cell death [124,125]. Phosphorylation/inactivation of GSK-3β, suppresses GSK-3β-dependent phosphorylation of tau at residues overphosphorylated in AD and prevents apoptosis of confluent cells. Treatment of cortical neurons with Aβ42 monomers increased Ser9 phosphorylation (inhibition) of the Akt substrate, GSK- 3β [97]. Inhibition of GSK-3β promotes cell survival through a variety of mechanisms including a reduced degradation of β-catenin, which then translocates into the nucleus and activates the transcription of protective genes [126].

4.2.3. Extracellular-signal regulated kinase 1/2 signaling (ERK1 and ERK2)—The mitogen-activated protein kinase (MAPK) family of protein kinases is traditionally viewed as important kinases in transmitting extracellular membrane signals intothe nucleus. The 44 kDa ERK1 and 42 kDa ERK2 are members of the MAPK superfamily that specifically respond to Aβ in brain cells [127]. ERK1 and ERK2 are known to be activated through dual phosphorylation by the MAPK/ERK on threonine and tyrosine in the Thr-Glu-Tyr sequence of the activation loop [128,129]. ERK signaling is critical for memory and tightly regulated by many proteins. ERKs are critical for human learning as revealed by human mental retardation syndromes [130]. They are also known to contribute to molecular information processing in dendrites, to stabilize structural changes in dendritic spines and to interact with scaffolding and structural proteins at the synapse [131]. ERK is an important neuronal marker for activity through activation by cytosolic calcium and depolarization of the membrane [132,133]. On phosphorylation and activation, ERKs phosphorylate other cytoplasmic effectors and are translocated into the nucleus where they phosphorylate transcription factors such as Myc, Fos, Jun, and Elk1 [104,134]. Direct substrates of the ERKs includetwo members of the RSK family of protein serine-threonine kinases, RSK1 and RSK2. The transcription factor CREB is phosphorylated on serine 133 *in vivo* by RSK2 in NGF-stimulated PC12 cells [135]. The dependence of CREB phosphorylation on activation of the ERK pathway is suggested by inhibition of Aβ-induced phosphorylation of CREB by piceatannol and the MEK inhibitor PD98059. Other kinases, such as protein kinase A (PKA) or Ca^{2+}/calmodulin-dependent protein kinases [CAM kinases; 136] may also contribute to phosphorylation of cyclic AMP response element (CRE)-binding protein

(CREB) in response to Aβ but the complete inhibition of CREB phosphorylation by PD98059 suggests that the ERK pathway is the main signaling pathway elicited by Aβ leading to transcriptional activation through CREB [137]. These data provide a mechanism by which Aβ alters gene expression through the transcription factor CREB [137], possibly resulting in a ceiling of activation that limits further formation of new memories.

4.2.3. Protein kinase C—PKC is part of a multigene family of serine-threonine kinases central to many signal transduction pathways [138] with a prominent role in memory [139]. It is likely that Aβ-induced increases in cytosolic Ca^{2+} signals are transmitted to PKC for PKC-mediated transcriptional activation. In addition, PKC activates ERK by interacting with Ras or Raf-1 [140] to initiate CREB phosphorylation. While PKC levels decline in AD [141], their activation restores K^+ channel function in cells from AD patients [142]. In addition, activation of PKC directly or indirectly enhances the α-processing cleavage of APP [143]. The activation of PKC has also been shown to prevent Aβ toxicity in rat primary hippocampal neurons [144].

4.2.4. Calcium signaling—Synaptic activity is required for neurons to survive[145] by entry of appropriate amounts of Ca^{2+} through synaptic NMDA receptors and other Ca^{2+} channels [146]. The process implicates key protein effectors, such as CaMKs, MAPK/ERKs, and CREB. Properly controlled homeostasis of calcium signaling not only supports normal brain physiology but also maintains neuronal integrity and long-term cell survival. Ca^{2+} signaling pathways can suppress apoptosis and promote survival through two mechanistically distinct processes. One process involves the PI3K/AKT signaling pathway which promotes survival [147]. The other pathway requires the generation of calcium transients in the cell nucleus which offers long-lasting neuroprotection [146,148]. Malfunctioning of calcium signaling to the cell nucleus may lead to neurodegeneration and neuronal cell death [149].

Dysregulation of intracellular calcium signaling has been implicated in the pathogenesis of Alzheimer's disease [150]. Aβ is known to act through multiple targets [151] including Ca^{2+} channels and various receptors in membranes. Synthetic Aβ binds to the calcium permeable nAChRs with high affinity [152]. Aβ42 administered in the low picomolar range activates nAChRs at presynaptic nerve endings of synaptosomes [83,153]. Under normal conditions, activation of nAChRs is necessary for the Aβ-induced increase in synaptic plasticity and memory [23]. However, it remains to be determined whether these effects are mediated by a direct physical interaction of the peptide with the nAChR. In addition, Aβ enhances transmitter release by transient increase of glutamate release from the presynaptic terminal that results from brief periods of high frequency stimulation with Ca^{2+} buildup within the terminal that triggers mechanisms of short-term synaptic plasticity [154].

Aβ directly interacts with Ca^{2+} channels such as voltage-dependent calcium channels (VDCC) and TRP cation channels (TRPC) to produce a transient increase in Ca^{2+} necessary for synaptic plasticity and neuronal survival. Aβ interacts directly with the recombinant L-type Ca^{2+} channel (α1C) subunit to increase Ca^{2+} channel protein at the cell membrane and hence increased Ca^{2+} conductance [80]. Within the TRPC subfamily, TRPC3 and 6 have been shown to protect cerebellar granule neurons against serum deprivation–induced cell death in cultures and promote neuronal survival in rat brain [155]. A neuronal survival mechanism of Aβ may also involve altered expression of K^+ channels [80]. In cerebellar granule neurons, 24-h pre-incubation with 1 μM unaggregated Aβ protein resulted in a 60% increase in the 'A'-type component of K^+ current possibly reflecting Ca^{2+}-mediated gene expression [156]. A full understanding of these signal transduction pathways of Ca^{2+} may lead to refined pharmacological strategies that minimize deadly effects of Ca^{2+} entry and optimize its growth- andsurvival-promoting properties.

4.2.5. Transcriptional activation—CREB is one of the best characterized stimulus-induced transcription factors that activate transcription of target genes in response to a diverse array of stimuli, including neuronal activity, a variety of protein kinases such as protein kinase A (PKA), MAPK/ERKs, pp90 ribosomal S6 kinase (RSK), and Ca^{2+}/calmodulin-dependent protein kinases (CaMKs). These kinases all phosphorylate CREB at a particular residue, serine 133 (Ser133) which is required for CREB-mediated transcription [157]. In contrast to CaMKs, ERKs cannot directly phosphorylate CREB. Two related RSKs and mitogen- and stress-activated protein kinases (MSKs) transmit the signal from activated ERKs to CREB [158]. CREB has been shown to be involved in certain types of hippocampal LTP as well as long-term memory, neurogenesis and synaptogenesis [159,160]. Transcriptional activation of CREB recruits a multiprotein assembly called a transcriptional co-activator complex. These often include proteins with intrinsic acetyltransferase activity [161]. Among the best characterized transcriptional co-activator proteins is CREB binding protein (CBP) [162]. A role for CBP in memory storage was first demonstrated in a mouse model of Rubinstein-Taybi Syndrome [163]. There is no direct evidence indicating how lower levels of Aβ might initiate CREB phosphorylation principally by Ca^{2+} signaling and/or through PKA/Atk/ERK pathways. However, exceeding physiological levels of Aβ could deregulate Ca^{2+} signaling mechanism by excessive accumulation of Ca^{2+} in the cytoplasm and cytoplasmic organelles such as mitochondria. Since hippocampal neuronal calcium is one of the most potent signals in neuronal gene expression [149], Aβ-induced Ca^{2+} deregulation may lead to compromised synaptic function. Consistence with this hypothesis, AD has been associated with impaired cAMP signaling which may contribute to the pathophysiology of the disease. Levels of the activated (i.e. phosphorylated) form of CREB are reduced in AD compared to that of an age-matched healthy control group [164]. Calcium signaling to the cell nucleus is the key inducer of CREB phosphorylation on its activator site serine 133 [165]. Experiments in aged neurons show altered calcium signaling at the level of either calcium signal generation and/or calcium signal propagation [166]. These studies indicate a critical role of calcium in Aβ-induced synaptic activity and memory formation by regulating specific signal transduction pathways.

4.3. Cholesterol transport

High cholesterol levels have been linked to overproduction of Aβ and are a risk factor for AD. One of the physiological functions of Aβ has been suggested to control cholesterol transport [167]. Prevalence of AD is reduced among people treated with inhibitors of cholesterol biosynthesis, statins [168,169] and animal studies support these results [170]. In vitro and in vivo studies have shown that cholesterol modulates APP processing and affects APP mRNA expression [171]. Another mechanism is the increased binding of Aβ to ApoE4 over non-E4 alleles. ApoE is a lipid and cholesterol transport protein responsible for the efflux of cholesterol from neurons to form stable complexes both in vitro and in vivo [172]. Allele ApoE4 is a major risk factor in AD [173]. This relationship might promote synaptogenesis, since in vitro studies have demonstrated that cholesterol released by astroglia increases synaptogenesis [174,175] with resulting modulation of spike rates [176]. Together, this evidence indicates that one of the physiological functions of APP might be to control cholesterol movement across neuronal membranes [167].

4.4. Antioxidant

The three histidine residues in Aβ control the redox activity of iron, indicating that Aβ is likely to be an important antioxidant. Aβ40 at 5 μM was found to protect primary neuronal cultures from the neurotoxicity of iron [94]. Nakamura et al. [177] found that Aβ40 or Aβ42 inhibits Fe^{3+} or Cu^{+2}-catalyzed ascorbate oxidation and hydroxyl radical generation. Nanomolar concentrations of Aβ can block neuronal apoptosis following oxidative damage,

which suggests that Aβ has a protective role against oxidative stress [178] and is essential for neuronal survival [28,94]. Monomeric Aβ40 was found to protect neurons cultured in a medium containing 1.5 μM Fe^{2+} without antioxidant molecules. However, the antioxidant protection of monomeric Aβ40 depends on the type of oxidant used. Aβ40 inhibits cultured neurondeath caused by Cu^{2+}, Fe^{2+}, and Fe^{3+} but does not protect neurons against H_2O_2-induced damage [94]. In cerebral cortical neuronal cultures, monomeric Aβ40 inhibits the reduction of Fe^{3+} induced by vitamin C and the generation of superoxides and prevents lipid peroxidation induced by Fe^{2+} [94]. Moreover, monomeric forms of Aβ42 also exhibited antioxidant and neuroprotective effects. However, oligomeric or aggregated Aβ40 and Aβ42 were devoid of such antioxidant activity and their neuroprotective activity was demolished. Thus, depriving neurons of the protective activity of Aβ42 monomers may also be an important factor in neurodegeneration [97]. These findings provide novel insights on a normal antioxidant role of Aβ and indicate that monomeric Aβ protects neurons by quenching metal-inducible oxygen radical generation and thereby inhibits neurotoxicity.

5. Effects of Aβ on dendritic spine plasticity and synaptic function

Synapse loss is thestrongest anatomical correlate of the degree of clinical impairment in AD [179]. Loss of dendritic spines at the sites of excitatory synaptic transmission may be the major pathological mechanism in Alzheimer's disease. However, issues regarding the level of Aβ concentration, type of Aβ species as well as the mechanisms of its production and actions that lead to synaptic loss remained poorly understood. Continuous overproduction of Aβ at dendrites or axons acts locally to reduce the number and plasticity of synapses [76,180]. The majority of excitatory synapses in the brain are made on the heads of dendritic spines [181]. Initially, synapse degeneration begins at the level of dendritic spines, the loci of memory-initiating mechanisms [182,183,184]. As seen in AD and transgenic mouse AD models, significant decreases occur in spine density [185,186,187,188], molecules involved in spine signaling [189,190] and control of filamentous actin (F-actin) [191]. In a mouse model for AD, the vicinity of amyloid plaques is characterized by highly dysmorphic neurites and spine turnover [192,193] causing a net loss of spines. These abnormalities in dendritic spines develop even before appearance of clinical symptoms in AD, likely because of cognitive reserve [187]. This phenotype could be caused by Aβ oligomers, which have been shown to block LTP and directly induce LTD, spine loss and memory loss [50]. Soluble oligomers of Aβ have a direct synaptotoxic effect at nanomolar concentrations [51]. In hippocampal culture, the soluble Aβ produced abnormalities in spine composition, shape, and abundance that strongly support the hypothesis that soluble Aβ initiates toxic mechanisms in AD brains that account for synaptic damage [74]. Continued exposure to Aβ caused abnormal spine morphology, with induction of long thin spines, loss of spine cytoskeletal protein drebin and a significant decrease in spine density [74]. In a direct investigation of the acute effects of extracellular and intracellular Aβ42 peptides on synaptic transmission, Moreno et al. [194] noticed inhibition of synaptic transmission by nanomolar concentrations of intra-axonal oligomeric Aβ42, but not oligomeric Aβ40 or extracellular oligomeric Aβ42. Similar nanomolar levels of Aβ disrupt hippocampal LTP [60,195]. Importantly, physiological concentrations of Aβ in extracellular fluids are picomolar [196]. Thus, local dendritic and axonal abnormalities associated with amyloid deposits lead to loss of synapses and the breakage of dendrites and axons in AD [187,193]. As dendritic spines are the major connecting elements of one neuron with another in the brain, changes in spine plasticity would have a detrimental impact on disease pathogenesis and progression. Overall, the accumulation of soluble or fibrillar amyloid deposits in AD causes disruption of synaptic connections on a permanent basis and this likely contributes to the cognitive decline and memory [197]. This decreased synaptic activity leads to the elimination of synapses and loss of network activity [198,199].

The molecular mechanism of spine loss by Aβ is not clear. Electron microscopic studies demonstrate that oligomeric Aβ is localized within the synaptic compartment [200] or that it is bound to the extracellular surface of the spine suggesting that oligomeric Aβ may interact directly at the synapse to cause dysfunction and spine collapse [201]. Soluble Aβ causes abnormal expression of Arc, a synaptic memory related protein that causes abnormal spine shape and glutamate receptor trafficking [42,202]. Aβ treatment of cultured hippocampal neurons leads to the inactivation of PKA and persistence of its regulatory subunit PKAIIα [203]. Since glutamate treatment reduces phosphorylated CREB phosphorylation and the decrease is reversed by rolipram (a phosphodiesterase inhibitor that raises cAMP and leads to the dissociation of the PKA catalytic and regulatory subunits), a similar mechanism may inhibit LTP by Aβ. Later studies confirmed the activation of the PKA/CREB pathway in both cultured neurons and murine hippocampal slices after inhibition of LTP by Aβ [204,205]. Interestingly, the toxicity of micromolar fibrillar Aβ on cultured neurons correlates with an age-related increase in phosphorylated extracellular signal-regulated kinase (pERK) as well as an age-independent over-activation of pCREB [7]. Aβ-induced activation of ERK1/2 may reduce mitochondrial respiration and ATP production by decreasing complex I activity and substrate oxidation through complex I [206]. Oligomers can also compromise synaptic function by altering the permeability of neuronal membranes and disrupting ion homeostasis [207,208]. None of these studies of action of Aβ on protein kinases have identified the proximal target of Aβ. However, these observations suggest that Aβ acts directly on the pathways involved in the formation of late LTP. Agents that enhance the cAMP/PKA/CREB-signaling pathway have potential for the treatment of AD [203]. These studies clearly support the emerging view that impaired synaptic function may be more important for the development of AD than neuronal cell death which occurs at later stages of the disease [199]. However, the major question of how abnormal spine dynamics and alterations in spine plasticity contribute to the disease progression in AD is still not very clear. The major challenge to prevent such loss in spine plasticity could prove invaluable for the treatment of neurodegenerative diseases.

6. Molecular targets of Aβ induced synaptic dysfunction

The search for a mechanism by which Aβ impairs synaptic plasticity has led to the identification of the cell surface receptors and signaling pathways mediating Aβ-induced synaptoxicity. Cell surface interaction sites reported for Aβ include receptor for Advanced Glycation End products (RAGE) and NMDAR [152,209]. Aβ has been variously reported to directly affect the activity of NMDAR, possibly by binding to nAChRs, or intracellular mitochondrial cyclophilin D (CypD), mitochondrial Aβ alcohol dehydrogenase (ABAD) or certain protein kinases. Examination of the evidence for these multiple activities of Aβ and their affinity constants may distinguish direct binding partners from downstream effectors.

6.1. NMDA receptors

It is well known that excitatory synapses contain AMPA and NMDA ionotropic glutamate receptors as well as metabotropic type glutamate receptors (mGluRs) positioned on dendritic spines [210,211]. Aβ-induced synaptic dysfunction has been attributed to the synaptic removal of AMPA receptors (AMPARs); however, it is unclear how Aβ induces this loss [212]. Glutamatergic processes are strongly implicated in causing and mediating the symptoms of AD [213]. The clinical use of memantine in treatment of AD provides direct support for the involvement of NMDARs in the cognitive deficits [214]. Memantine acts as a low-to-moderate affinity open channel uncompetitive inhibitor of NMDARs at therapeutic concentrations [215,216]. Aβ promotes glutamatergic excitotoxicity and potently disrupts glutamatergic synapses and plasticity providing an explanation for the cognitive deficits in AD [217]. Aβ alters the glutamatergic transmission system by inducing marked reductions in levels of AMPA and NMDA receptors at the neuronal plasma membrane [74,75,218,219].

At physiological levels, Aβ selectively enhances NMDAR-mediated currents and synaptic transmission [220,221]. While increased Aβ application promotes endocytosis of NMDARs in cortical neurons and produces a rapid and persistent depression of NMDA-evoked currents in cortical neurons [75]. This reduction of NMDAR-dependent currents is thought to result from Aβ-mediated activation of nAChRs [75]. Aβ can also promote increased Ca^{2+} influx and elevate the levels of potentially toxic reactive oxygen species in an NMDAR-dependent manner [221,222]. In general, brief periods of high synaptic activity open NMDARs, leading to a long-lasting increase in postsynaptic AMPAR number, spine growth and LTP of synaptic transmission [223,224,225]. Snyder et al. [75] reported a pathway by which Aβ reduces glutamatergic transmission and NMDAR – dependent LTP. The application of Aβ42 to cultured cortical neurons promoted endocytosis of NMDARs, effectively reducing the density of NMDARs at synapses. At higher concentrations, Aβ is known to enhance activation of NMDARs [226] and cause NMDAR agonist-induced delayed cognitive dysfunction [227]. It is apparent that excessive or inappropriate activation of NMDAR can block LTP [228,229].

Alternatively, low levels of synaptic stimulation can activate NMDARs to produce NMDA-dependent or mGluR-dependent LTD. These two forms of LTD can induce removal of postsynaptic AMPARs and loss of spines [230,231,232,233]. Interestingly, sublethal NMDAR activation increased the production and secretion of Aβ [65,234]. However, some of the conceptually and biomedically most important questions that have arisen from these novel insights concern the molecular mechanisms by which Aβ and the glutamatergic transmission system cooperate at the synapse to synergistically regulate and control synaptic transmission. Is excitotoxicity that results from excessive glutamate receptor activation the main trigger that increases the secretion of Aβ during synaptic transmission or is Aβ solely a pathologic product directing cell demise? It is possible that the increased Aβ production causes an increase in NMDA activation and increased NMDA activation in turn increases the Aβ production within limits. This process would have a negative impact on synaptic function if there were a homeostatic balance between NMDA activation and Aβ production. However, excess NMDA activation or excess Aβ generation both are harmful for synaptic plasticity that could lead to the cognitive impairment in AD.

Treatment with Aβ oligomers also causes reduction of post-synaptic density-95 (PSD-95), an adaptor protein that plays a critical role in synaptic plasticity and in the stabilization of AMPAR and NMDAR at synapses [218]. Dysregulation of NMDAR function causes excessive neuronal Ca^{2+} influx, oxidative stress [222], and inhibition of the Wnt/β-catenin signaling pathway [235,236].

6.2. Nicotinic acetylcholine receptors (nAChRs)

Activation of the neuronal pentameric nAChRs is involved in diverse brain functions including synaptic plasticity and memory [237,238] and enhances transmitter release in several brain regions including the hippocampus [239], the spinal cord dorsal horn [240], the olfactory bulb, and the amygdala [241]. The increase of synaptic plasticity by Aβ requires activation of nAChRs [242]. Because activation of nAChRs is necessary for the Aβ-induced increase of synaptic plasticity and memory under normal conditions, Aβ may modify glutamate release with a mechanism dependent upon activation of nAChRs [83]. However, several reports of the effect of Aβ42 on nAChRs are conflicting. Some studies have reported that Aβ42 activates nAChRs [243,244], while others indicate that Aβ42 inhibits nAChRs [245,246]. For example, physiological levels of Aβ can activate while toxic levels inhibit presynaptic nAChR and evoke changes in presynaptic Ca^{2+} levels in rat hippocampus and neocortex [244]. Interestingly, picomolar concentrations of Aβ42 were effective in activating nAChRs while higher levels of Aβ produced inhibitory action. The disparity may depend on the nanomolar Aβ1–42 inhibition of nicotine-induced Ca^{2+} responses while

picomolar Aβ42 directly evokes sustained increases in presynaptic Ca^{2+} via nAChRs [244]. Aβ42 binds to the nAChR with picomolar affinity [247]. This binding can modulate presynaptic, glutamate-mediated synaptic transmission or glutamate release, suggesting that Aβ42-dependent cholinergic modulation activates signal transduction mechanisms that ultimately result in synaptic transmission and memory consolidation [248]. However, it remains to be determined whether these effects are mediated by a direct physical interaction of the Aβ peptide with the nAChRs. Immunohistochemical studies on human sporadic AD brains show that Aβ42 and nAChR, are both present in neuritic plaques and co-localize in individual cortical neurons suggesting that Aβ could be tightly associated with nAChR [247]. Alternatively, Aβ might be responsible for regulation of nAChR function through strong binding with membrane lipids [249]. Picomolar or higher Aβ42 acting through nAChRs, can elicit ERK MAPK activation in hippocampal cultures [245,250] possibly triggered by Ca^{2+} influx [243,251]. ERK is known to regulate transcription factors such as CREB and Elk-1 by phosphorylation [140], which help initiate transcription of memory-associated genes that contain their respective regulatory elements [252]. Therefore, over-activation of nAChRs and excessive Ca^{2+} influx or dysregulation of Ca^{2+} homeostasis provide a molecular mechanism for the cholinergic dysfunction that is a hallmark of AD [253,254].

6.3. Mitochondrial cyclophilin D

Mitochondria serve as direct targets of neuronal toxicity in which Aβ associates with the outer mitochondrial membrane, inter-membrane space, inner mitochondrial membrane, and the matrix [255]. Progressive accumulation of Aβ in cortical mitochondria in AD patients and also in brains from transgenic AD type mouse models suggests a role for mitochondrial Aβ in the pathogenesis or development of the disease. Once inside the mitochondria, Aβ is able to interact with a number of targets, including the mitochondrial proteins ABAD and cyclophilin-D (CypD) [256]. Opening the mitochondrial permeability transition pore (MPTP) to depolarize mitochondria and release cytochrome C may be central to mitochondrial and neuronal malfunction in AD patients [257]. CypD, an integral part of the MPTP, whose opening leads to cell death, interacts with Aβ peptide within the mitochondria of AD patients and a Tg mouse model of AD [258]. MPTP causes mitochondrial swelling, outer membrane rupture, release of cell death mediators and enhances production of reactive oxygen species (ROS). Computer simulation studies show that Aβ interacts with both ANT and CypD [259]. CypD/Aβ interaction causes an oxidative stress and increased MPTP opening that triggers neurodegeneration [258]. CypD-deficient cortical mitochondria are resistant to Aβ- and Ca^{2+}-induced mitochondrial swelling and MPTP opening [257]. Adenine nucleotide translocase (ANT) is a transport protein for ADP and ATP and component of MPTP that binds directly to CypD [260]. This interaction may facilitate its anchoring in the inner membrane and disturbance of the mitochondrial membrane potential, mitochondrial swelling and cell death [259]. Interestingly, the MPTP also requires the participation of members of the Bcl-2 family proteins but a clear understanding of the interaction of Aβ with CypD together with both proapoptotic or antiapoptotic Bcl-2 family proteins in AD has not been made. The ability of CypD to protect neurons from Aβ- and oxidative stress-induced cell death and its role in improvement of synaptic and cognitive functions has been suggested to provide a new therapeutic approach for the treatment of conditions associated with AD. Together these studies provide new mechanisms for Aβ targets that link the MPTP to synaptic stress and the neurodegeneration seen in AD.

6.4. Mitochondrial Aβ-binding alcohol dehydrogenase (ABAD)

ABAD is a member of the short chain dehydrogenase reductase family in mitochondria that binds Aβ [261]. Binding of Aβ to ABAD distorts the enzyme's structure, rendering it inactive. Binding also promotes mitochondrial generation of free radicals. In neurons,

ABAD is predominately localized to mitochondria. Upon binding ABAD, Aβ triggers events leading to neuronal apoptosis through a mitochondrial pathway [262,263]. Mitochondrial Aβ levels in the 3xTg-AD mouse increase significantly at 9 months and temporally correlate with increased levels of Aβ binding to ABAD [264]. Interestingly, mitochondrial ABAD is upregulated in neurons from AD patients [263]. The ABAD-Aβ complex has been hypothesized to induce oxidant stress and mitochondrial dysfunction [265]. Increased expression of ABAD exacerbates Aβ-mediated mitochondrial and neuronal stress [263,266]. Aβ binding to ABAD causes free radical production and neuronal apoptosis [267]. Neurons cultured from transgenic mice with targeted overexpression of a mutant form of amyloid precursor protein and ABAD (Tg mAPP/ABAD) displayed spontaneous generation of hydrogen peroxide and superoxide anion, and decreased ATP, as well as subsequent release of cytochrome c from mitochondria and induction of caspase-3-like activity followed by DNA fragmentation and loss of cell viability [266]. In addition, cytochrome c oxidase (COX) activity was selectively decreased in neurons cultured from mAPP/ABAD mice. In vivo, mAPP/ABAD mice displayed reduced levels of brain ATP and COX activity, diminished glucose utilization, as well as electrophysiological abnormalities in hippocampal slices compared with mAPP mice [266]. ABAD-Aβ binding and enhanced generation ofoxidants in brain mitochondria of transgenic mice results in exaggerating neuronal stress and impaired learning and memory [268]. Analysis of hippocampal slices from mAPP/ABAD mice were shown to display diminished LTP compared with other genotypes [266]. However, positive effects of low levels of Aβ have not been studied. Similar to CypD, the ABAD-Aβ interaction may also represent a novel treatment target against AD. Other intra-mitochondrial targets of Aβ remain to be discovered. These data suggest that mitochondrial ABAD, ordinarily a contributor to metabolic homeostasis, has the capacity to become a pathogenic factor in an Aβ rich environment.

7. Redox and phosphorylative energetic exhaustion: Aβ-induced mitochondrial and synaptic dysfunction

Increasing evidence indicates that the mitochondrial dysfunction is an important early factor in the development of AD-like pathology [264]. Mitochondria are known to accumulate in synapses [269,270] and mitochondrial trafficking to synapses is dynamic and regulated by synaptic activity [271]. However, increasing evidence indicates that accumulation of Aβ in mitochondria occurs before extracellular amyloid deposition and increases with age. Aβ has been found in the mitochondria of both AD brain and transgenic mouse models of AD overexpressing Aβ [255,256,272,]. Aβ has been detected in mitochondria from postmortem brain specimens of AD patients [255] and also in isolated mitochondria from the cerebral cortex of APP transgenic mice [272]. APP and its derivatives, monomeric and oligomeric forms of Aβ, interact with mitochondrial membranes [263,272,273,274] or mitochondrial matrix protein ABAD [264] leading to mitochondrial dysfunction. Accordingly, Aβ is linked to the mitochondrial malfunction observed in the Alzheimer's disease brain and mouse models of AD [255,272]. Substantial evidence indicates that mitochondria serve as direct targets for Aβ protein mediated neuronal toxicity.

Studies of postmortem brains from AD patients and transgenic mouse models of AD suggest that mitochondria are involved in oxidative damage induced by Aβ early in AD progression [reviewed in reference 275]. Lower levels of ROS are required for synaptic signaling with ROS acting as messenger molecules in the process of LTP [276]. However, high levels of ROS have been implicated as damaging toxic molecules in the age-related impairments of LTP [276,277]. Our previous work shows that ROS levels increase with age of neurons in parallel with an age-related decline in transmembrane potential [278]. As mitochondrial transmembrane potential is a driving force for cellular production of ATP, its decline in neurons will have a long term effect in many important energy driven reactions. Increased

oxidative stress, coupled with dysregulation of calcium homeostasis and resulting apoptosis of vulnerable neuronal populations, are proposed to underlie the loss of synaptic activity and associated cognitive decline [275]. From these deficiencies emerges the concept of synaptic energy exhaustion in AD, both phosphorylative (ATP) and redox (NAD[P]H) energies. Our previous work shows that hippocampal NAD(P)H and glutathione (GSH) decline with age in association with increased susceptibility to glutamate toxicity in neurons of old-age [279]. Thus, an age-related decline in neuronal reducing currency (NAD[P]H) and reducing buffer (GSH) will surely promote oxidative stress and excess ROS. It is noteworthy that in the early stages of AD, there is already a reduction in the number of mitochondria [280] and the activities of tricarboxylic acid cycle enzymes [281] and cytochrome C oxidase [282]. However, how ROS are produced at the synapse in response to Aβ oligomers is not fully known. Excessive ROS are locally generated in response to synaptic Aβ oligomer binding [222]. This ROS formation can be totally blocked by the mitochondrial uncoupler, 2,4-dinitrophenol which suggests a central role of mitochondria in Aβ-induced oxidative stress [222]. Many studies suggest the possible involvement of oxidative stress and calcium dysfunction in Aβ toxicity [283,284]. Experiments with *Caenorhabditis elegans* containing inducible Aβ42 indicate that oxidative stress can precede fibrillogenesis [285]. These reports were strengthened by findings that Aβ toxicity at the synapse is dependent on the presence of a functional mitochondrial electron transport chain which is a principal site of ROS formation as well as a major target for their deleterious effects [286].

The question as to why brain synaptic ROS levels increase with age is uncertain, but may involve lack of use [287] followed by acute overstimulation of excitatory NMDARs that leads to excessive ROS, related to excess Ca^{2+} entry into mitochondria [288]. Dysregulation of NMDAR function induced by Aβ binding to neuronal synapses may lead to synaptic mitochondrial dysfunction and excessive ROS formation [222,289]. Memory mechanisms might be directly compromised by elevated ROS, which could explain the connection between AD and oxidative stress [222]. The increase in oxidative damage exhibited by synaptic mitochondria will damage synapses, affect neurotransmission and might be ultimately responsible for cognitive decline in AD patients. Taken together these studies provide convincing evidence for the concept that mitochondria have a pivotal role in Aβ-induced synaptic dysfunction and neuronal stress. Improved function of mitochondria is an effective way of reducing effects of aging and may inhibit neuronal cell death in AD [287].

8. Conclusions

The present review highlights some important physiological roles for Aβ in the CNS during normal function and AD pathogenesis. Given the important role that Aβ plays in various activities at the synapse, Aβ should not be regarded merely as a toxic factor that requires eradication to avoid dementia. There is enough evidence to suggest an essential activity-dependent role of Aβ in modulation of synaptic activity and neuronal survival. However, dissociation of the synaptic effects of aging from Aβ remains to be investigated. Several extracellular and intracellular synaptic receptors are important targets of Aβ oligomers. Alterations in receptor characteristics and synaptic dysfunction are crucial to the early memory deficit and cognitive decline in AD. Alterations in synaptic plasticity, mitochondrial function and neurotransmission by Aβ can affect activity-dependent signaling and gene expression, resulting in the disintegration of neural networks and, ultimately, the failure of neural functions [290]. These ongoing discussions provide new insights into strategies for development of AD therapy that not only reduce the amount of Aβ but also inhibit Aβ aggregation and restore mitochondrial and redox energy for synaptic function.

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Abbreviations

ABAD	mitochondrial Aβ-binding alcohol dehydrogenase
Ca^{2+}CAM	Calcium calmodulin
CAMKIV	Calcium/calmodulin-dependent protein kinase type IV
CREB	Cyclic AMP response element (CRE)-binding protein
CBP	CREB binding protein
CypD	cyclophilin D
ERK	extracellular signal-regulated kinase
Fas	FS7-associated cell surface antigen
FOXO	forkhead transcription factor
GSK	glycogen synthase kinase
Grb2	growth factor receptor-bound protein 2
IR	insulin receptor
IRS-1	insulin receptor substrate-1
IRS-2	insulin receptor substrate-2
LTP	Long term potentiation
mitDH	mitochondrial dehydrogenases
MEK	MAPK kinase, MAPK, mitogen-activated protein kinase
MPTP	membrane permeability transition pore opening
mTOR	mammalian target of rapamycin
α7-nAChR	α7-nicotinic acetylcholine receptor
NMDAR	N-methyl-D-aspartic acid receptor
PDK1	3-Phosphoinositide-dependent kinase 1
PI3K	phosphoinositide 3′ kinase
PKB/Akt	protein kinases B
ROS	reactive oxygen species
VDCC	voltage-dependent calcium channels
TRPC	TRP cation channel

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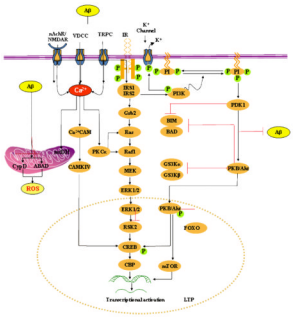

Fig. 1. Model of picomolar Aβ-induced insulin-PI3K-Akt-ERK signalling plus mitochondrial targets of intracellular Aβ

Extracellular Aβ at picomolar concentration binds to the insulin receptor (IR) and activates PKB/Akt via PDK-1. PKB/Akt translocates into the nucleus and phosphorylates CREB. Activation of the lipid kinase PI3K is critical for the activation of PKB by PDK. PDK1 phosphorylates the activation loop of a number of protein serine/threonine kinases of the AGC kinase superfamily, including protein kinase B (PKB α; also called Akt1). Akt may also maintain the integrity of the mitochondria by a unknown mechanism or by a specific mechanism of Bad phosphorylation. Akt can also inhibit apoptosis by phosphorylation and inactivation of caspase-9. ERK1/2 are activated by upstream MAPKK, such as MEK1/2, and MAPKKK, such as c-Raf. MEK1/2 induce ERK1/2 activation via dual phosphorylation on threonine 202 and tyrosine 204 residues. Phosphorylation of ERK leads to the activation of a number of transcription factors, important in controlling differentiation, neuronal survival, learning and memory plasticity. For example, ERK activates pro-survival transcription factor CREB, by activating both p90RSK and MSK1/2.

Picomolar extracellular Aβ also binds nAChR, glutamate receptors (NMDAR) and Ca^{2+} ion channels (e.g. VDCCs, TRPC) and causes Ca^{2+} influx at controlled rates into the cytoplasm and mitochondria. Increased cytosolic calcium concentrations initiate the activation of several kinase-dependent signalling cascades including activation of PKC leading to CREB activation and phosphorylation at Ser133, a process critical for protein synthesis-dependent synaptic plasticity and LTP. PKC-α also activates ERK by interacting with Ras or Raf-1. Mitochondria are critical targets of intracellular Aβ. Aβ interacts with CypD, a protein component of the membrane permeability transition pore (MPTP). The interaction of CypD with Aβ causes functional modification of this protein leading to MPTP opening. Aβ also binds with another mitochondrial protein, ABAD to distort the enzyme's structure, rendering it inactive. This causes an increase in reactive oxygen species and oxidative stress leading to initiation of apoptosis.

Table 1

Neuron survival and memory functions of Aβ peptides.

Peptide	Form	Source	Concentration (nM)	Function	Reference
Aβ1-40	monomer	Synthetic	10 μM	Inhibits formation of Aβ1-42 β-sheets	94
Aβ1-40	monomer	Synthetic	0.1–10	Neurotrophic for E18 rat neurons	98
Aβ1-40 & Aβ1-42	Monomer or mixed	Synthetic	0.01–1	Increases rat cortical neuronal cell viability	28
Aβ1-40 & Aβ1-42	Mono + oligomers; anti-Aβ antibody	Synthetic	0.1	Rat memory formation & consolidation	248
Aβ1-40 & Aβ1-42	monomer	Synthetic	1–10; 1–1000	Increased survival (PI- 3K, AKT) and protection from NMDA toxicity	97
Aβ1-42	monomer	Synthetic	0.2	Enhanced LTP in mouse hippocampal slices + improves mouse memory by ICV injection	83
Aβ1-42	Monomers +oligomers	Synthetic	0.01–1	Inhibited nicotine- evoked increases of Ca^{2+} in rat synaptosomes	153