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Neuro-pathological Implications of β-Amyloid Protein: An Update

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β-Amyloid protein has been extensively and mostly exclusively associated with Alzheimer's Disease (AD) since past many years. Its relation to other neuro-pathologies is still elusive. The present work begins with the review of AD connection of β-Amyloid protein and further looks at various studies that establish its role in other neuro-pathological disorders like glaucoma and Parkinson's Disease (PD). It further searches for the possibility of its involvement in neuroblastoma and brain tumors. Only recent and/or context relevant studies have been included.

β-AMYLOID PROTEIN AND ITS PRECURSOR

β-Amyloid protein (A beta) is a starchy, amorphous appearing, 39-43 amino-acid containing peptide [1]. In 1984, Glenner and Wong isolated and purified this protein and suggested it to be a cleaved product formed from a precursor protein [2]. The precursor protein from which β-amyloid protein is derived, is a transmembrane glycoprotein that is expressed ubiquitously and is known as amyloid precursor protein (APP) [3]. On the basis of X-ray diffraction, β-amyloid protein structure has been reported to be composed of an antiparallel β-sheet [4-6] with polypeptide chains being separated by a distance of 4.76 Å while the adjacent sheets are 10.6 Å apart [6]. The fibrillary axis is perpendicular to the β-strand but parallel to the cross linking hydrogen bonds [7-8]. Residues 1-28 in the β-amyloid protein comprise the hydrophilic domain while the C-terminal 12-14 residues form the hydrophobic domain [9]. The β-amyloid protein is formed by modification in its precursor known as amyloid precursor protein (APP). The APP is a member of family of conserved type 1 membrane proteins [10] and is quite a complex molecule with its extracellular part being larger in comparison to the intracellular portion [11]. APP gene in human is located on the long arm of chromosome 21 and has 18 exons [12, 13]. The alternative splicing of APP mRNAs encodes different isoforms ranging from 365 to 770 amino acid residues, with specific types of the resultant isoforms being formed in specific tissues. However, the functional relevance of such tissue specific alternative splicing is not well understood [10].

In the precursor molecule of β-amyloid protein APP, the hydrophilic domain represents the extracellular part while the hydrophobic domain represents the part of cell membrane [9]. Not just β-amyloid protein but many other fragments (eg. secreted APP alpha) are formed following many different pathways from APP that perform variety of functions that are neuroprotective, neurotrophic and regulatory however much of the functional aspect of these fragments remain unexplored and unknown [11]. Also the functions of full length APP are not well understood, however there have been studies showing its importance in neural functions like regulation of cell excitability, synaptic transmission, long term potentiation and more, indicating towards its involvement in regulation of behavioral learning and memory [11]. The full length APP has been suggested to act as cell surface receptor similar to notch [14]. It is even suggested to act as a ligand to β-amyloid [15, 16]. There have been evidences which support the notion that the extracellular domain of APP regulates β-amyloid production and downstream signaling by binding to a neuronally secreted glycoprotein that is, F-spondin [17]. There are few other reports about the interaction of APP with proteins like netrin-1 [18], Nogo-66 [19], that have role in neuronal cell signaling and β-amyloid production respectively. Thus, there have been increasing evidence of involvement of APP in various aspects of functions of the nervous system [10].

Considering the formation of β-amyloid from APP and its clearance, an important point to mention is that it is expressed at a high level in the brain and it is quite rapidly metabolized that too in very complex ways [20]. The precursor molecule APP breaks down to form β-amyloid and other fragments as well. Under normal conditions, the APP is transiently expressed in the cell membrane having a short half-life and it is cleaved within the region of β-amyloid protein leading to no formation of intact β-amyloid protein fragment [21]. Under abnormal conditions on the other hand, cleavage of APP occurs in such a way that a nearly 4 KDa intact β-amyloid fragment is released that is responsible for AD pathology [21].

Broadly, there are two pathways of cleavage of APP- (a) the non-amyloidogenic pathway, in which APP is cleaved by α- and γ-secretases and (b) the one in which APP is cleaved by β- and γ-secretase enzymes that produces many different types of fragments of β-amyloid [22] (**Figure 1**). The main β-secretase enzyme in brain is β-site APP cleaving enzyme 1 (BACE 1), which cleaves APP initially to pro-

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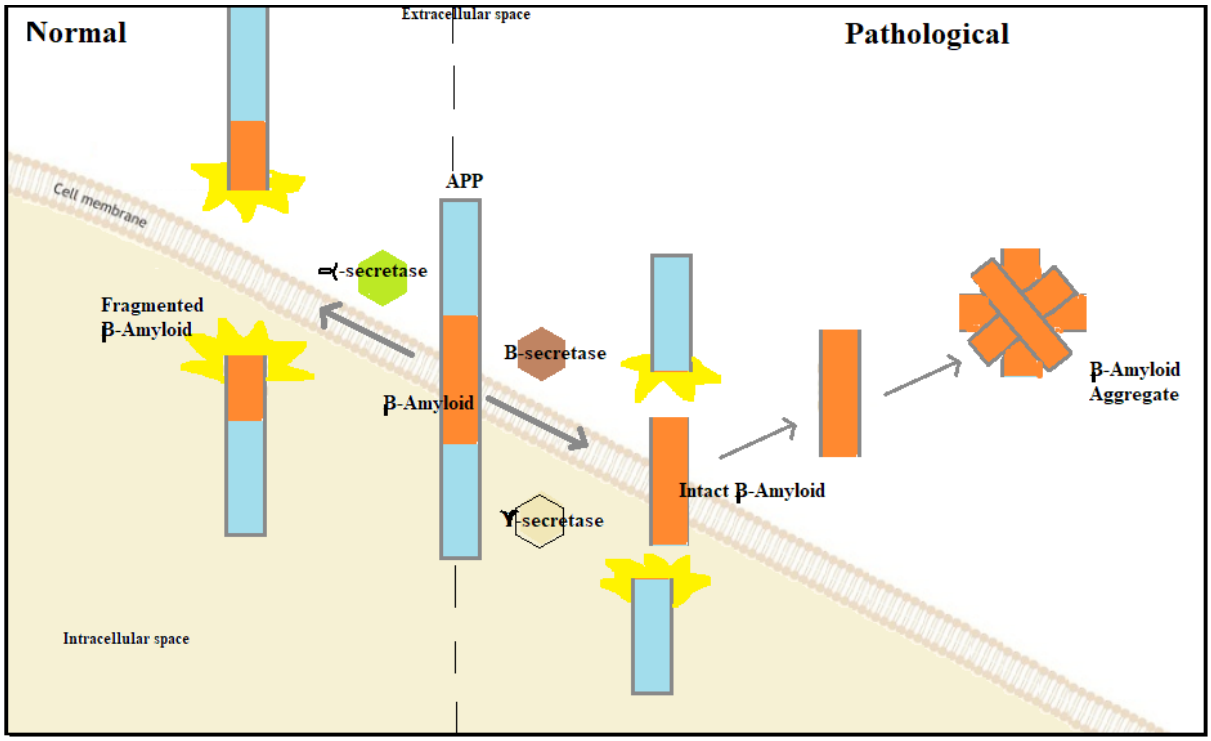

Figure 1. Fragmentation of APP under normal (healthy) conditions and formation of β-amyloid protein aggregates in pathological conditions.

duce C99 fragment and soluble APPβ. The C99 fragment is further acted upon by γ-secretase to form β-amyloid [23-26]. Since the proteolytic function of γ-secretase is regulated by PSEN1 (presenilin 1) and PSEN2 (presenilin 2), any mutation in these regulatory proteins affects the activity of γ-secretase causing increased β-amyloid production that ultimately leads to AD [27]. There are different mechanisms of clearance of β-amyloid protein such as receptor mediated clearance, degradation by enzymes [28-31]. So, there is a constant turnover of β-amyloid in the brain maintaining a steady state but any imbalance in the production and clearance of β-amyloid leads to its accumulation and finally senile plaques, the characteristic structures of AD are formed.

EFFECTS OF β-AMYLOID ON NEURONS

β-Amyloid exists in multiple assembly states and inflicts variety of physiological or patho-physiological effects. It was earlier considered to be deposited extracellularly, but studies done in human and mice show that it also accumulates intra-neuronally and contributes to progress of disease [32]. β-Amyloid is formed in the perikarya of neurons and is transported to the axon termini [33]. More recently, researchers have opined that in comparison to extracellular plaques, the sites of deposition of excess β-amyloid, the soluble oligomeric β amyloid is the major factor causing damage [34, 35]. This notion further gets support from the finding that extracellular plaques do not correlate with cognitive dysfunction associated with alzheimer's disease while soluble oligomers do [36]. It is believed that only soluble oligomers can insert themselves in to lipid bilayer where they form alpha helices to start the production of ROS that ultimately leads to protein oxidation and lipid peroxidation [37].

However, many studies still propound that extracellularly deposited form of β-amyloid is also responsible for damage and disease [38, 39]. Whether β-Amyloid is secreted in the extracellular regions or forms dimers, trimers, oligomers intracellularly, it inflicts the neurons in a variety of ways. Extracellular β-amyloid forms aggregates that ultimately form the core of senile plaques. β-Amyloid plaques enhance oxidative stress and also increase β-amyloid monomers and small oligomers that can cause neuronal damage [38]. Further β-amyloid can accumulate in the membrane of mitochondria and induce production of free radicals that can decrease the activity of mitochondrial complex IV. This can reduce ATP formation leading to mitochondrial dysfunction and death of neurons [33]. The oxidative stress can affect the lysosomal activity of removal of toxic proteins and can inactivate the proteasomal (especially 26S) system also that is responsible for toxic protein aggregates [40]. On the basis of studies done in cell lines, hippocampal neurons, transgenic animal models and post-mortem data, β-amyloid oligomers have been suggested to cause mitochondrial dysfunction, inflammation, ER stress, calcium dysregulation [41, 42]. Accumulation of phosphorylated tau protein in the neurons is atypical feature of alzheimer's neurodegeneration that contributes to synaptic dysfunction and degeneration of axons [43, 44]. Phosphorylation of tau causes formation of two stranded and interwined neurofibrils in neurons [45] which are responsible for disintegrating microtubules, structural loss and malfunction in the neurons [46] (**Figure 2**).

ROLE OF β-AMYLOID PROTEIN IN ALZHEIMER'S DISEASE

Alzheimer's disease (AD), first reported by Alois Alzheimer in 1907 is a progressive neurodegenerative disease characterized by senile dementia that is, progressive cognitive deterioration along with inability to perform normal activities of day to day life [20]. Since there is an increase in the life expectancy, the number of people affected with

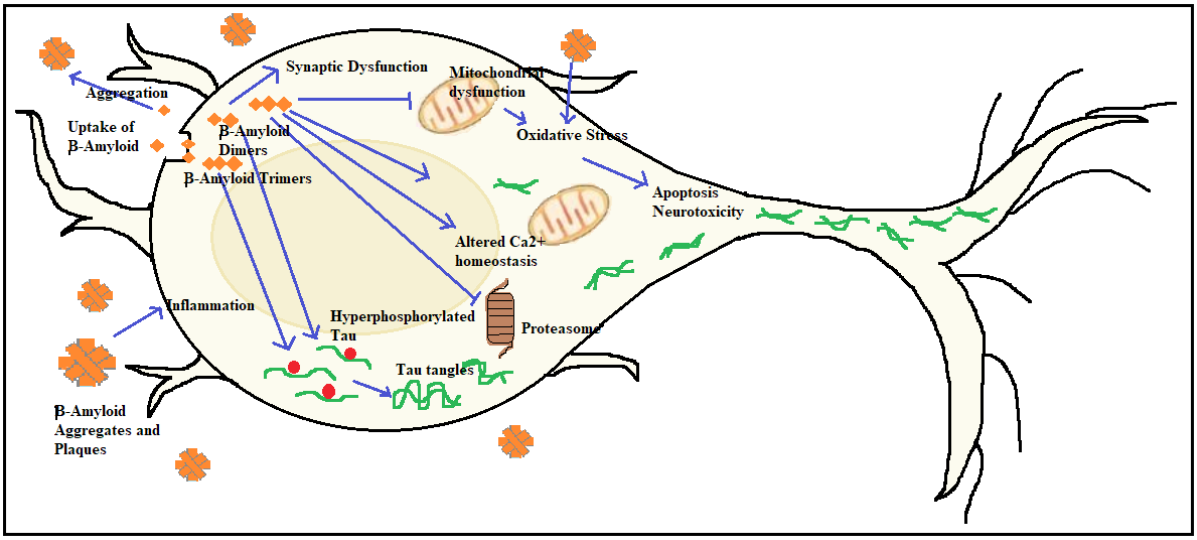

Figure 2. A neuron showing effect of extracellular and intracellular β-Amyloid peptides on its different cellular functions.

AD is obviously going to get raised [47]. It has been speculated that nearly 10% of people above the age of 65 years suffer from AD and this percentage will further escalate as the population ages [21]. It is expected to affect about 106.8 million people all over the world by the year 2050 [48]. β-amyloid has largely acquired a central role in the AD studies since last few decades as it has been proposed to be the common initiating factor of pathogenesis of AD according to the amyloid cascade hypothesis [10]. AD involves mental deterioration due to progressive neuronal loss from specific regions of the brain, neurofibrillary tangles in dead and dying neurons along with formation of plaques that contain amyloid [49]. In AD, the β-amyloid peptides mainly accumulate extracellularly in the center of the senile plaque [50], that is a complex lesion of cortical neuropil with size nearly 50μm having a central core of extracellular amyloid fibrils surrounded by dystrophic neurites, activated microglia and reactive astrocytes. The misfolded β-amyloid accumulates in the neuronal ERs and extracellular regions [51]. β-amyloid is the major protein component of the core but some other proteins are also associated with the senile plaques like apo-lipoproteins, acute phase proteins, glycosaminoglycan containing proteoglycans [47]. Molecular chaperones however, have been found to suppress the formation of neurofibrillary tangles by preventing tau aggregation [52]. It has been demonstrated in cellular models of AD that elevated levels of Hsp90 and Hsp70 promote solubility of tau and tau binding to microtubules thereby causing a reduction in insoluble tau and tau phosphorylation [52]. Role of another protein called α-synuclein (a presynaptic protein necessary for neuronal plasticity [53]) has also remained debated as some studies suggest that it plays important role in β-amyloid aggregation while others suggest that α-synuclein is absent in the senile plaques that occur in AD [54].

There have been strong genetic evidences that show key role of β-amyloid in pathogenesis of AD. Point mutation and double mutation in the APP flanking or within the sequence lead to early onset of inherited form of AD, as observed in many families [55-58]. Mutated amyloid proteins that are associated with AD form annular protofibrils that are similar to a class of pore-forming toxins of bacteria, indicating that membrane permeabilization in an inappropriate way may lead to cell dysfunction and death in AD [59].

After so many studies done since last two decades, the exact role of β-amyloid in the AD patho-mechanism is still debated. Current opinion about this issue is that oligomers of β-amyloid in soluble form and not in the fibrillar form in the neuritic plaques may be responsible toxicity at an early stage and may also be initiating the pathological process [60].

ROLE OF β-AMYLOID PROTEIN IN PARKINSON'S DISEASE (PD)

Parkinson's disease (PD) or "shaking palsy" as described first by Dr.James Parkinson in 1817 is a progressive, chronic neurodegenerative disease exhibiting both motor and non-motor characteristics [61]. Parkinsonism is a symptom complex in which there is bradykinesia, tremors in resting condition, muscular rigidity etc due to neuronal loss in both dopaminergic and non-dopaminergic regions [61]. Considering the molecular pathways underlying the pathogenesis of sporadic and familial PD, there are many evidences which indicate that mitochondrial function deficits, oxidative and nitrosative stress, ubiquitin-proteasome system dysfunction and accumulation of misfolded proteins may be involved [62]. Amyloid deposits are also a characteristic feature of Parkinson's disease (PD) [63]. Recent data have been indicating that β-amyloid protein is associated with PD also. Mastaglia et al (2003) had found that vascular and parenchymal β-amyloid deposition may contribute to cognitive decline and dementia when other factors like deposition of α-synuclein in cerebral cortex and formation of cortical lewy bodies are also present [64]. β-amyloid can act as a predictive biomarker of cognitive decline associated with PD as β-amyloid is found in CSF of PD patients [65]. Neurofibrillary tangles containing β-amyloid protein were observed by Ito et al (1991) in entorhinal cortex of patients having parkinsonism-dementia complex of Guam (PDC) [66]. PD is also reported to be a brain amyloid disease like the AD however, in case of PD cytoplasmic amyloid bodies are present which are referred to as lewy bodies [67]. Lewy bodies are characteristic pathological lesions occurring in

substantia nigra neurons in PD [68]. A major component of the lewy bodies is α-synuclein [69] that have capacity to aggregate and form filaments. The filamentous lesions found in PD are typically made of α-synuclein [70]. The location of α-synuclein protein accumulation is within the neurons inside lewy bodies and lewy neurites [49]. It has been found in cell free system that β-amyloid peptides promote the aggregation of α-synuclein while in cell culture it promotes intra-neuronal accumulation of α-synuclein [71]. Thus, on the basis of the results obtained by Masliah et al (2001), it became evident that β-amyloid plays significant role in the progression of α-synuclein dependent neuronal pathologies such as PD as it promotes the aggregation of α-synuclein [71]. In a similar way to that of AD, mutant amyloid proteins related to PD form annular protofibrils similar in structure to each other that elicit inappropriate membrane permeabilization like bacterial toxins and may cause cellular dysfunction and death in PD [58]. Another factor contributing to PD progression is formation of misfolded proteins and presence of unfolded proteins. In brains of patients of neuro-degenerative disorders, stress proteins are expressed and are found to be associated with protein aggregates frequently [72]. Also, around the degenerative regions in patients' brains, activated glial cells are found. Both, stress proteins and glial cells may regulate the neuronal death along with acting as intracellular molecular chaperones and exhibiting chaperoning neuronal activity [72]. Hence their dysfunction may lead to neuro-pathological implications. There are many evidences indicating that β-amyloid and α-synuclein may be interacting to cause damage to the plasma membrane and mitochondria when the protofibrils are translocated to the membranes [50]. Accumulation of β-amyloid and α-synuclein oligomers in membranes of mitochondria may cause release of cytochrome C and eventually activate the apoptotic cascade [50]. On the contrary, mitochondrial dysfunction and oxidative stress that increase permeability of the membrane and cause cytochrome C release, may promote β-amyloid and α-synuclein oligomerization and neuro-degeneration [50]. It has also been demonstrated that α-synuclein that can form amyloid readily *in vitro* without any co-factors and can also initiate the formation of tau amyloid [73]. After this initiation, tau and α-synuclein can synergize polymerization of each other [73]. Also, the elevated levels of β-amyloid in the brain can enhance formation of aggregates of α-synuclein amyloid and tau [73].

ROLE OF β-AMYLOID PROTEIN IN GLAUCOMA

Glaucoma is a multifactorial neuro-degenerative ocular disorder in which loss of retinal ganglion cells takes place leading to permanent irreversible loss of vision. Its pathogenesis at mechanistic level is still elusive. Many similarities have been observed in its progression with that of AD. Not only this, the amyloidogenic pathway has also been identified as a target for developing novel neuro-preotective therapies for glaucoma [74, 75]. Janciauskiene and Krakau (2001) have suggested that β-amyloid protein is a potential link between AD, exfoliation syndrome and glaucoma [76]. An earlier study done by Morin et al (1993) established that APP synthesis occurs in the retinal ganglion cells and it is transported in the form of small transport vesicles in the optic nerve. Then it is transferred to the plasma membrane of the axons and nerve terminals where it gets metabolized (half-life = less than 5 hours) [77]. An immunoreactivity based study showed that β-amyloid and APP are distributed in higher levels in various regions of the ocular hypertensive retinas in C57BL/6 mice which may be due to abnormality in APP splicing and increased intra-ocular pressure [78]. Presence of significant deposition of β-amyloid protein and phosphorylated tau protein in the retinas of glaucoma patients indicates strong involvement of these proteins in glaucomatous pathogenesis. A recent study done in chronic glaucoma model established in rhesus monkeys has shown AD like pathologies such as deposition of β-amyloid and p-Tau in the lateral geniculate nuclei of glaucomatous eyes [79]. Weak expression of β-amyloid was also found in the primary visual cortex [79]. High intra-ocular pressure (IOP) is a very significant factor in glaucoma causation and it has been found to induce formation of β-amyloid [80]. Activation of caspases (-3 and -8) along with formation of β-amyloid by abnormal APP processing have been shown to be playing important role in the pathophysiology of glaucoma in rat model [80]. β-amyloid formation may be important in stress response towards glaucomatous neurodegeneration [74]. An increased level of β-amyloid in retina may impair the synaptic circuitry and retrograde traffic of neurotrophic factors in the ON axons [81, 82]. Although the actual cause of the death of retinal ganglion cells in glaucoma is not known but changes in function of the synapses due to impairment precedes the death of retinal ganglion cells [83]. Thus, it can be speculated that β-amyloid leads to retinal cells' impairment and degeneration in glaucoma [84]. Wilson et al (2016) have also suggested on the basis of their study done in DBA/2J mouse models of glaucoma, that elevated levels of β-amyloid protein in early stages of glaucoma may increase the susceptibility of the retinal ganglion cells to future stressors [85]. They have also suggested that β-amyloid is not associated with structural aberrations of the cytoskeleton of retina in glaucoma but may be playing active role in axonal transport deficits [85]. β-amyloid oligomers have been associated with decreased pace of axonal transport [86], increased spectrin breakdown products and pathological phosphorylation of tau, neurofilament-heavy chain (NF-H) [87] by activating kinases like glycogen synthase kinase-3b [88]. The induction of hyper-phosphorylation of tau by β-amyloid alters the integrity of retinal cells and their synapses in inner nuclear layer [88].

Another implication of elevated levels of β-amyloid fibrils in the eye is increase in the concentration of intracellular calcium [89], which modulates activation of calpain. The activation of calpain is responsible for specific cleavage of structural proteins such as spectrin and neurofilaments [90]. β-amyloid accumulation together with that of tau are also known to cause mitochondrial dysfunction and formation of reactive oxygen species [91]. Study done by Guo et al (2007) presented strong evidence for involvement of β-amyloid in causing experimental glaucoma as apoptosis of RGCs was observed in *in vivo* conditions [74]. They also suggested that upon targeting β-amyloid and blocking its effect by combinational therapy can be a potent anti-glaucoma therapy [74]. A very recent study came up

with a new hypothesis according to which dysfunction of the glymphatic pathway that is involved in clearance of interstitial solutes including β-amyloid out of the brain, plays important role in the glaucomatous pathogenesis [92].

ROLE OF β-AMYLOID PROTEIN IN NEUROBLASTOMA

Neuroblastoma is extracranial solid tumour which grows from immature nerve cells. It mostly arises in and around adrenal gland, abdomen, chest and neck and near the spine where nerve cell clusters are present. It starts very early, during embryonic stage and is mostly reported in infants and young children and seldom in later stages of life [93]. Most common cause of neuroblastoma is increase in reactive oxygen species (ROS) [94] which are chemically active atoms or molecular fragments that bear charge due to an excess or deficiency of electrons. Few studies have reported that oxidative stress induces intracellular β-amyloid production. For instance, oxidative stress induced in human neuroblastoma SH-SY5Y cells on treatment with H_2O_2 is reported to increase intracellular levels of β-amyloid Protein. 250 μM H_2O_2 exposures resulted in significant decline in levels of full length β-amyloid precursor protein and its carboxyl terminal fragment which is generated by β –cleavage [95]. On the other hand, accumulation of β-Amyloid Protein is liable for production of free radicals and thus leading to impairment of mitochondria and cytoskeletal, exhaustion of ATP, and finally apoptosis. So it can be said that a cyclic form of cause-effect-cause relation exists between β-amyloid and oxidative stress and both these factors contribute to neuroblastoma causation. Supplementation with pool of antioxidants: Folate, vitamin E, and acetyl-l-carnitine are able to provide protection against oxidative insultarising due to exposure of human neuroblastoma cells to β-amyloid [96]. Oxidative stress due to amyloid protein also affects sulfhydryl groups in membrane calcium pumps. Human neuroblastoma cells (SH-SY5Y) stably transfected with human wild-type amyloid precursor protein (APP) showed reduction in activity of mitochondrial ETC complex IV whereas activity of complex III was significantly boosted in APP cells as compared to control. APP cells displayed mutilation in activity of total respiration and decline in ATP production [97]. Methionine-35 side chain of the β-amyloid plays an important role in its neurotoxicity. This has also been experimentally demonstrated by Clementi et. al., 2006 in IMR-32 cells (Neuroblastoma cells) treated with three different amyloid peptides namely, native amyloid peptide (having Met-35 in reduced state), modified peptide with oxidized Met-35 and derivative having Met-35 substituted with norleucine. Native peptide was more potent in decreasing cell viability as compared to peptide with oxidized Met-35 whereas peptide in which Met-35 was substituted with norleucine did not show toxic effects. Native form of peptide caused downregulation of anti- apoptotic protein bcl-2 whereas level of apoptotic markers Bax and caspase-3 were elevated [98].

Further, primary cultures of rat cortical neurons (SH-SY5Y cells) differentiated by a 7-day exposure to 10 μM retinoic acid treated with amyloid peptide at a concentration of 25 μM for 24, 48, or 72 h is found to result in increase in the number of cells in the S phase and reduction in the population of the G2/M, along with stimulation of programmed cell death. These effects are known to be regulated by activation of mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK1/2) pathways [99]. β-Amyloid peptide induces oxidative stress that is associated with the membrane, which causes functional impairment of different receptors, transporters, ion channels, transcription factors and downstream kinases [100]. Synapses are quite sensitive to abnormal protein aggregates and impairment of synaptic signaling may lead to apoptotic cascades [100]. Not just oxidative stress and mitochondrial dysfunction, but ER stress and proteasomal dysfunction are also the implications of aggregation and deposition of misfolded proteins like α-synuclein, tau, β-amyloid that eventually lead to neuronal death [101]. Thus, a number of studies show that exposure of amyloid peptide to neuroblastoma cells *in vitro* upsets mitochondrial respiration, cell cycle, generation of ATP and also induces oxidative stress.

ROLE OF β-AMYLOID PROTEIN IN PRION DISEASES

Prion diseases, also called as Transmissible Spongiform Encephalopathies (TSEs) are fatal neurodegenerative disorders that inflict CNS of human and other mammals. Examples include Bovine spongiform encephalopathy, Crutzfeldt Jacob disease (CJD), etc. Abnormal protein aggregation outside as well as inside the cells, is a typical feature of major neuro-degenerative disorders including prion diseases also [100]. Among all the neurodegenerative disorders, prion diseases form a distinctive group as these are transmissible and infectious in nature, with the infectious particles being present in exosomes for spreading prion infectivity within the cells [102]. Typical neurodegenerative disorders like AD and PD are also referred to as “prion like diseases” as these share few neuropathological features with the prion diseases [103].

The causative agent of prion diseases is considered to be scrapie prion protein (PrP^{Sc}), that is formed by misfolding of normal PrP^{c}, and has the capacity to self-propagate exponentially and precipitate in to insoluble amyloid aggregates that cause neuronal death [103, 104]. The PrP^{Sc} is a β-sheet rich pathogenic isoform produced by conformational conversion of alpha-helix rich physiological GPI anchored isoform PrP^{c} [104]. Interactions between β-amyloid and PrP^{c} protein has been reported in some relevant studies and have shown the involvement of β-amyloid in prion disease pathogenesis also. Many *in vitro* and *in vivo* studies suggest that aggregated and misfolded β-amyloid peptide that triggers AD pathology manifests all the major features of typical mammalian prions [105]. Both β-amyloid seeds and PrP-prions are resistant to formaldehyde and heat [106-109] and both agents are excessively long-lasting in living brain [110]. Further, recent studies indicate that prion protein (PrP^{c}) mediates a fraction of toxicity of β-amyloid oligomers [111]. β-amyloid oligomers have been reported to interact with PrP^{c} and mGluR5 leading to modulation of toxicity and neuronal death in AD. In the same study it has been suggested that mGluR5 is critical in prion disease

also [112]. As already mentioned in the above sections that oxidative stress is generated due to β-amyloid that in turn, leads to more oxidative stress. This generation of oxidative stress due to β-amyloid is not only associated with etiology of AD, ALS, PD, multiple sclerosis but also with prion diseases viz. CJD, bovine spongiform encephalopathy, Kuru etc. [113]. These studies thus indicate a pathological overlap between prion diseases and prion like diseases (AD, PD etc) with β-amyloid being an important player.

CONCLUSION

β-amyloid is conclusively a complex insoluble molecule with unclear nature, behavior, structure and pathological roles. It is an important participant in pathogenesis of many neurodegenerative diseases, but its exact functions are not revealed yet. It is clear that it affects many physiological aspects of neurons such as oxidative status, mitochondrial function, ER function, to name a few but complete understanding of participation and other associated aspects still remains elusive, thus having many research prospects.

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Notes

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