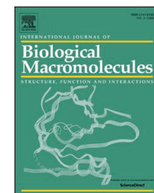
International Journal of Biological Macromolecules 190 (2021) 44–55

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: www.elsevier.com/locate/ijbiomac



Review

The role of amyloids in Alzheimer's and Parkinson's diseases

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A R T I C L E I N F O

Keywords:
Amyloid fibrils
Amyloid oligomers
Alzheimer's disease
Parkinson's disease
α-Synuclein

A B S T R A C T

With varying clinical symptoms, most neurodegenerative diseases are associated with abnormal loss of neurons. They share the same common pathogenic mechanisms involving misfolding and aggregation, and these visible aggregates of proteins are deposited in the central nervous system. Amyloid formation is thought to arise from partial unfolding of misfolded proteins leading to the exposure of hydrophobic surfaces, which interact with other similar structures and give rise to form dimers, oligomers, protofibrils, and eventually mature fibril aggregates. Accumulating evidence indicates that amyloid oligomers, not amyloid fibrils, are the most toxic species that causes Alzheimer's disease (AD) and Parkinson's disease (PD). AD has recently been recognized as the 'twenty-first century plague', with an incident rate of 1% at 60 years of age, which then doubles every fifth year. Currently, 5.3 million people in the US are afflicted with this disease, and the number of cases is expected to rise to 13.5 million by 2050. PD, a disorder of the brain, is the second most common form of dementia, characterized by difficulty in walking and movement. Keeping the above views in mind, in this review we have focused on the roles of amyloid in neurodegenerative diseases including AD and PD, the involvement of amyloid in mitochondrial dysfunction leading to neurodegeneration, are also considered in the review.

1. Introduction

With the huge life style changing process and increased life spans, the modern world witnessed a great worldwide increase in neurodegenerative diseases including Alzheimer's disease, Parkinson's diseases, and Prion's disease. It is therefore very important to understand their molecular origin and mechanism, so as to be able to discover rational therapeutic strategies to fight the diseases and find cures for them. Interestingly, the process of transformation of normal soluble proteins into amyloid fibrils is now accepted to be a generic property of a polypeptide chain. In the early 1990s research showed that several familial mutations in the gene lysozyme gave rise to a fatal form of systemic amyloidosis [1–3], highlighting this globular antibacterial enzyme into the group of proteins associated with protein-misfolding diseases [1–3].

Studies also reported that these mutations in lysozyme significantly augmented the possibility of protein misfolding, which altered the protein into pathogenic amyloid fibrils [4]. Similarly, mutations in other amyloidogenic proteins, including amyloid β (Aβ), α-synuclein, and prion protein increase the propensity to form Alzheimer's disease, Parkinson's disease, and Prion's disease, respectively. Other factors which also promoted protein misfolding in amyloidogenic proteins are changes in the environmental conditions (pH, temperature, or protein concentration), posttranslational modifications, increases in the rate of degradation, errors in trafficking, loss of binding partners, and oxidative damage. All of these factors can act either independently or simultaneously [5].

These amyloids are formed from partially unfolded or misfolded intermediates of Aβ which are particularly prone to aggregation, in particular at high peptide concentrations. These intermediates, including the partially misfolded intermediates, aggregate by interacting with complementary intermediates through exposed hydrophobic residues and form oligomers and, consequently, protofibrils and fibrils.

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https://doi.org/10.1016/j.ijbiomac.2021.08.197
Received 26 January 2021; Received in revised form 23 August 2021; Accepted 26 August 2021
Available online 2 September 2021
0141-8130/© 2021 Published by Elsevier B.V.

It is interesting to note that these intermediates do not cross-polymerize or aggregate. Furthermore, these amyloid fibrils accumulate as amyloid deposits in the brain and central nervous system in Alzheimer's disease (AD), Parkinson's disease (PD), and prion's disease. Moreover, it has been shown that these different types of neurodegenerative diseases occur via different mechanisms [6–11]. Also, these aggregates are classified into two distinct structures: random amorphous structure and well-ordered amyloid fibril structure [12]. So far, the etiologies of AD, PD, and prion diseases remain unknown. Aβ deposited in AD patient brain, derives by sequential proteolytic processing of the amyloid precursor protein (APP) by β- and γ-secretases [13]. Aβ peptides aggregate to form insoluble fibrils, a major component of extracellular plaques in human brain. The aggregation of Aβ follows similar pathways as with other proteins that cause neurodegenerative diseases with the formation of small soluble nuclei that act as seeds and promote exponential fibril growth [14]. The assembly of monomeric proteins or peptides into smaller oligomeric structures is the rate-limiting step in fibril formation, in case Aβ, an important role of N-terminal modification was suggested in aggregation process [15]. Similarly, aggregation is a main pathogenic feature of α-synuclein in PD. However, aggregation propensities of α-Synuclein mutants and their correlation with PD are not straightforward due to the heterogeneous and unstable nature of these oligomeric/fibrils and due to protection conferred in cellular models of α-synuclein overexpression by reagents that inhibit or neutralize aggregated species [16]. α-Synuclein is an intrinsically disordered protein and shows remarkable conformational flexibility and adopts a range of conformations. In the process of fibril formation, various intermediate forms of α-synuclein develop with various degrees of potentiality to be neurotoxic. Mutant α-synuclein forms fewer protofibrils than the wild protein, whereas mutated and phosphorylated forms produce more mature fibrils indicating the diversity in propensity of forming different fibrillar species [16]. Although amyloid species have been generally considered as pathological entities, current accumulating evidence indicates that they might also play a functional role. These amyloid structures, or simply functional amyloids, conduct melanosome biogenesis, long term memory formation, and transfer the conformation-based information [13,17]. It has also been discovered that proteins with prion-like domains adopt amyloid-like folds which promote functional phase transitions/stress granule formation [14,18]. Amyloid fibrils are highly ordered structures that contain characteristic cross β sheet structural motifs. In the cross β-sheet structure, the β-sheet structure runs perpendicular to the fibril axis. These fibrils are composed of 2–6 unbranched protofilaments with a diameter of 2–5 nm, which is linked laterally or twisted together forming fibrils with diameters of 4–13 nm [15–17,19–21]. Each strand in β-sheet is in register with the neighboring strand and forms hydrogen bonds with the strands above and below the fibril. Amyloid fibril aggregates can interact with dyes such as Congo red, leading to birefringence, as well as Thioflavin-T, resulting in fluorescence.

Intrinsically disordered conformation of tau is also an important origin of different neurodegenerative diseases. Since the tau protein adopts intrinsically disordered conformation, its interaction with microtubule is impaired and it undergoes aggregation, leading to Alzheimer's diseases and several other neurodegenerative diseases. Keeping this in mind, we shed light on the role of amyloids in various types of neurodegenerative diseases and their treatments using varieties of small molecule drugs. The role of iron and nitric oxide in relation to amyloids and neurodegeneration, and the role of amyloid in mitochondrial dysfunction leading to neurodegeneration, are also explored.

2. Alzheimer's disease (AD)

AD is characterized by degeneration of pyramidal neurons in the basal forebrain and hippocampus. These events lead to the development of late onset dementia, and eventually loss of ability to carry out simple tasks, speech, and recognition [22]. The molecular basis of this disease pathology is highly debated. However, it has been suggested that three major risk factors are associated with AD. The primary factor is believed to be age, which is the root cause of the disease's development [23,24]. Gender is the next deciding factor, as the incidence of Alzheimer's disease is much more prevalent in women than in men, which cannot be simply attributed to the higher longevity of women versus men. The third factor is the ApoE4 allele [25,26], and among the persons diagnosed with AD, up to 60% carry at least one ε4 allele [27]. It is associated with deposition of visible precipitates of β-amyloid and tau in neuronal cells extracellularly and intracellularly, respectively.

Tau proteins (microtubule-associated proteins) are also known to be associated with other major neurodegenerative disorders known as 'tauopathies' [28]. However, their main role is to promote the assembly and stability of microtubules (MT) [29,30]. One study revealed that hyperphosphorylation of tau is one of the most important post-translation modifications that ultimately lead to aggregation. Briefly, in this process hyperphosphorylation changes the shape of intrinsically disorder tau protein, and as a consequence, it dissociates from the microtubules, undergoes aggregation, and gets deposited intracellularly, thus giving rise to AD. These aggregates of hyperphosphorylated tau protein are also known as paired helical filaments. However, the precise mechanism of tangle formation is not yet completely understood. Generic and sporadic cases have both been reported; however, mutations in the gene encoding the amyloidogenic protein are also responsible for misfolding and aggregation [31].

In the familial cases, autosomal dominant mutations in the *APP*, *PS1*, or *PS2* genes have been found to cause early-onset AD, and these account for around 3–5% of the total AD cases. These mutations increased the amount of amyloid peptide production and plaque formation [32,33]. Similarly, mice models for AD that expressed humanized APP with mutations related to familial AD also promoted aggregation of Aβ [34]. The acquired and genetic cases of AD have different timings of expression/manifestation of disease, with the genetic forms beginning earlier and progressing faster than the acquired forms, which are expressed lately and slowly [35]. Approximately 95% of the cases of AD are sporadic. The acquired forms of AD may also occur due to abnormal loss of Ubiquitin Proteasome System (UPS) [36] or because of high intrinsic disposition of some proteins to escape all protective mechanisms, thereby resulting in misfolding and aggregation [37].

It is therefore evident that formation of amyloid fibrils and their deposition in the brain is mainly responsible for Alzheimer's disease. Furthermore, in AD, amyloid precursor protein (APP) containing β amyloid peptide encompassing 42 amino acid residues is cleaved by an enzyme β-secretase, which is a beta-site APP-cleaving enzyme (BACE). The β amyloid peptide is further cleaved by another aspartyl protease, γ-secretase, which generates a set of Aβ peptides with length ranging between 38 and 44 residues, and where Aβ42 and Aβ40 are the most abundant species. The Aβ42 (amyloidogenic form) is more susceptible to aggregation reaction [38,39]. This peptide, which normally undergoes cellular degradation, forms extracellular aggregates owing to the formation of beta pleated sheet stabilized by extensive interchain H-bonding, and gives rise to amyloid fibrils and plaques formation in some patients [40]. In Aβ peptide, hydrophobic residues are present internally and are flanked by amino acids 17 (Leucine) and 21 (Alanine) which play a vital role in the early steps of Aβ misfolding and aggregation, indicating that hydrophobic interactions mainly drive Aβ assembly formation [41,42].

This is consistent with the findings that Aβ peptides possess much higher predisposition to form amyloid fibrils due to the presence of extra two or three hydrophobic amino acid residues at the carboxyl terminus [43]. In general, the location of amino acid substitutions plays an important role in protein aggregation reaction. For example, mutations that decrease the hydrophobicity of the nucleation site can also decrease the aggregation propensity or vice-versa [44–46]. Secondly, the net charge has also been speculated to form an important factor in protein aggregation. This is because, in the presence of high net charge of one

type, the protein experiences electrostatic repulsion culminating in partial unfolding, and therefore has a higher susceptibility to interact with other similar structures and consequently form amyloid fibrils, which are deposited in the brain extracellularly [47].

2.1. Structure of Aβ fibrils

The full-length Aβ fibrils structure is arranged in parallel fashion. The core structure of fibrils is stabilized mainly by the hydrogen bonds involving the polypeptide main chain. Since the main chain is common to all polypeptides, this observation explains why fibrils formed from different polypeptides showed significant similarities in their backbone structure [48,49]. However, it has been found that fibrils are polymorphisms in nature. The polymorphisms arise because of differences in the side chains packing. The structure of fibrils has been demonstrated by different methodologies, including transmission electron microscopy (TEM) and atomic force microscopy (AFM). These microscopic studies have shown that fibrils primarily consist of a number of (2–6) protofilaments, where each protofilament is about 2–5 nm thick in diameter. These protofilaments are often twisted around each other, to form a supercoiled rope-like structure, which is 7–13 nm wide [48]. These protofilaments may also associate laterally to form long ribbons, which are 2–5 nm thick and up to 30 nm wide [50,51].

Further studies using Circular dichroism, Fourier transform infra-red spectroscopy, solid-state NMR (nuclear magnetic resonance) (Fig. 2) [52] and X-ray fiber diffraction data have shown that each protofilament is arranged such that β-strands stack in register and run perpendicular to the long axis of the fibril, and generate a structure which is known as a cross-β structure [44,48]. In general, the core of most amyloid fibrils structure is dehydrated. This results from the packing of hydrophobic residues inside of amyloid fibrils that give rise to one of the 8 possible steric zipper arrangements [53]. These arrangements occur because there are 2 possible types of β-sheets including parallel or antiparallel, 2 types of stacking possibilities parallel or anti-parallel, and 2 surfaces for inter-sheet packing (face-to-face or face-to-back) (Fig. 3) [50,54]. Additional complexities in the fibril structure may also arise from quaternary interactions in which protofilaments containing a basic building block are bundled or twisted together to form a mature amyloid fibril [49,53].

2.2. Structure of protofibrils and annular aggregates

The structure of protofibril intermediates resembles to the mature fibrils. For instance, the structure of protofibril is elongated and linear in shape. However, these protofibrils lack the higher-order structure and periodicity present in the mature fibrils. In fact they are curvilinear, thinner (usually less than 10 nm in diameter), and shorter (usually below 400 nm in length) than fibrils [51,52,55,56]. The schematic diagram of protofibrils is shown in Fig. 1. These Aβ (1–40) protofibrils can interact with CR or ThT, but these interactions are weaker than those found in mature fibrils. This implies a lack of higher-order structure in the protofilament.

Spectroscopic studies including circular dichroism, infrared spectroscopy, and X-ray diffraction of proto-filaments revealed high contents of β-sheet structure [55–57]. The solid-state NMR of protofilament [58] has shown that each β-sheet structure contains two beta strands. Other aggregates, such as annular aggregates, consist of several oligomers which are arranged in a ring-like shape that encloses water molecules.

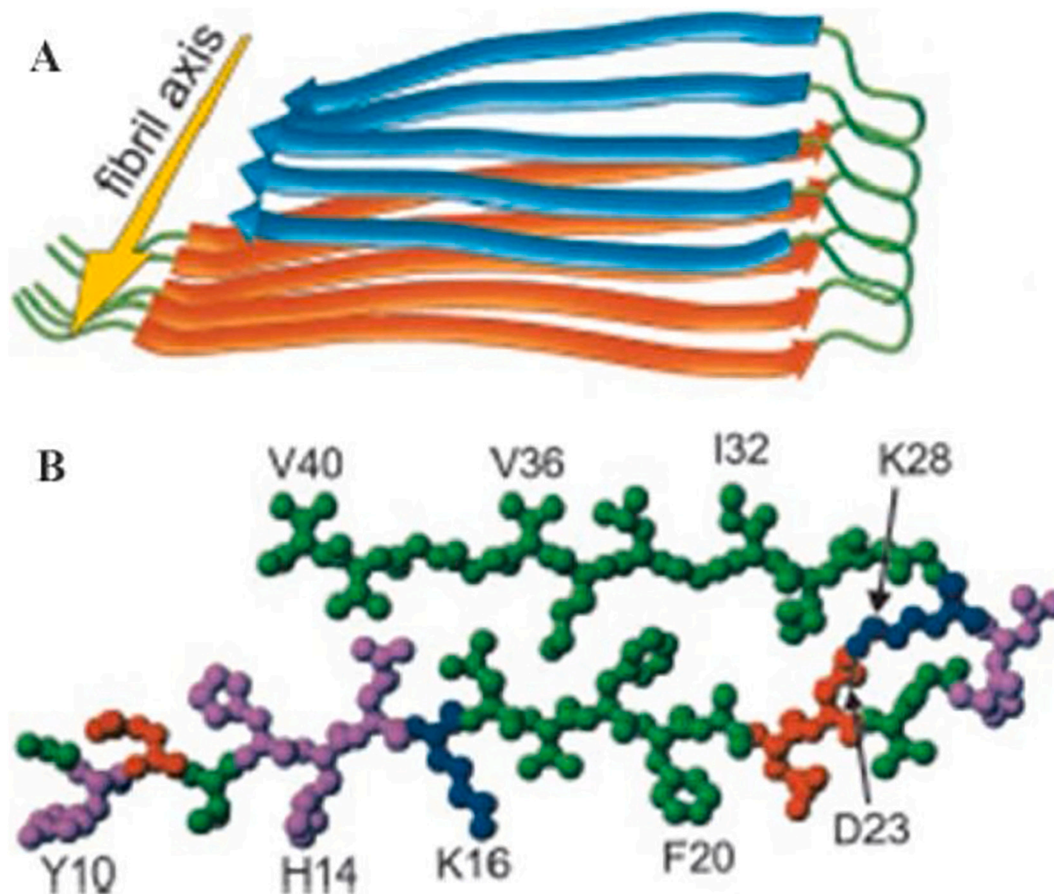

Fig. 1. Structural model for Aβ1–40 fibrils, consistent with solid state NMR.(A) Schematic representation of a single molecular layer, or cross-β unit.(B) Central Aβ1–40 molecule from the energy-minimized, five-chain system, viewed down the long axis of the fibril. Reprinted with permission from Petkova et al. [223]. Copyright 2002 PNAS USA.

The pathway and structures of different aggregated states are shown in Fig. 2. Thus, the structure of the annular aggregate is substantially different from mature fibrils and protofibrils [59]. The annular aggregates can be formed from variety of proteins including Aβ peptide and α-synuclein, as well as many other proteins [60–61]. However, the finer details of the structure of these annular aggregates are lacking. Available data indicate that they partly resemble pore-forming toxins, implying that these aggregates have a potential to compromise integrity of the cellular membrane. This was supported by the findings that annular aggregates possess membrane-perturbing activity [62].

2.3. Structure of amyloid oligomers

Although structural information of mature fibrils are available in abundance in literature, relatively little is known about the structure of non-fibrillar aggregates, oligomers. The structural characterizations of oligomers have been profoundly hampered mainly because these oligomers are heterogeneous in nature, undergo interconversions and are insoluble, which imposes enormous complications for the elucidation of the atomic resolution structure [63–66]. To solve these hurdles, researchers have invented a novel innovative approach, which consists of the use of small molecules, including detergents or lipids that trap or stabilize oligomeric species of amyloid proteins [67,68]. But these approaches have often led to off-pathway or non-productive intermediates, rather than on-pathway intermediates, which play a key role in amyloid disease [69].

In spite of these problems, a number of low-resolution structures of amyloid oligomers have been obtained using techniques such as transmission electron microscopy (TEM), atomic force microscopy (AFM), hydrogen/deuterium exchange, and fluorescence spectroscopy [66–69,70–73]. The AFM and TEM methodologies have consistently shown that most of the large oligomers are roughly globular in shape, or are annular, exhibiting a pore or ring shape [74–76]. The solid state NMR of large (15–35 nm) spherical Aβ (1–40) oligomers reveals fibril-like secondary and quaternary structures [77]. These oligomers exhibited neurotoxicity, and lie on the fibril assembly pathway. Further, under different solution conditions, discoidal pentamers and decamers of Aβ (1–42) were obtained which were also found to be neurotoxic [78]. Fourier-transform infrared (FTIR) spectroscopy and NMR analyses of small oligomers have convincingly shown that the same residues are involved in the formation of β-sheet structure in Aβ (1–40) oligomers and fibrils, and that the two states displayed similar FTIR spectral characteristics [79,80]. However, FTIR data indicate that the β-sheet structure of some Aβ (1–40) and Aβ (1–42) oligomers are antiparallel, whereas Aβ fibrils possess parallel β-sheet arrangements. Secondly, NMR experiments suggest that the β-sheet packing distance and assembly could be different in Aβ (1–42) oligomers and Aβ (1–42) fibrils. Thirdly, oligomers showed higher diffusibility, hydrophobicity, and ability to interact with membranes [81], which could explain how they cause toxicity.

2.4. X-ray structure of other amyloid oligomers

Most recently, the X-ray structure of stabilized oligomer containing 6 antiparallel β-sheets were identified in other amyloid-forming protein αB crystalline [82]. This oligomer adopts a cylindrical β-barrel structure. Similarly, hexamers of C-terminal fragments of amyloid-forming protein αB crystalline, notably Aβ (24–34), Aβ (25–35), and Aβ (26–36) adopted similar β-barrel oligomeric structures [83]. These Aβ fragments were shown to cause neuronal cytotoxicity and death by compromising the plasma membrane integrity. These small stable fragments can also forms large oligomers, adopting β-barrel structures.

Similarly, other protein pancreatic islet amyloid polypeptide (hIAPP) shows the conformational transition of soluble hIAPP into aggregated β-barrel structures. The penta- and hexa-peptide, hIAPP (23–27) and hIAPP (22–27) also form stable β-sheet-containing amyloid fibrils that differ completely in their final aggregated fibrillary assemblies [84]. Although hIAPP fibrils are associated with Type-II Diabetes, the relationship between the fibrillar/oligomeric forms to disease condition remains unsolved to date. The disease-causing mutation S20G of full length, as well as fragments, were much more prone to aggregation. The structure of hIAPP 19–29 S20G fragment forms cross β-sheets with inter hydrophobic interface as also observed for Aβ fibrils. These fragments showed cytotoxicity similar to full-length hIAPP fibrils. Contrarily, a similar segment, 15–25 of wild type, forms non-toxic labile β-sheets fibrils, thus highlighting the discrepancy in the propensity to form β-barrel oligomers as aggregation intermediates and amyloid cytotoxicity [85]. These discrepancies suggest that protein segment structures represent polymorphs of their parent protein, and can have different consequence in disease conditions.

2.5. Mechanisms of Aβ oligomers mediated toxicity

The mechanism underlying aggregation of Aβ to amyloid fibrils is currently not fully understood. Accumulating experimental data suggest that early aggregation intermediates in the form of soluble oligomers are the major neurotoxic components in this process. The mechanisms of Aβ oligomers in the pathogenesis of Alzheimer's disease have been explored in great detail. Recently, numerous reports have appeared that indicate an increase in membrane conductance or leakage in the presence of small globulomers to large prefibrillar assemblies [86]. Hence, this represents one of the mechanisms by which the Aβ oligomer causes toxicity to neuron cell. On the other hand, other studies suggest the formation of discrete ion channels or pores in the membrane [87,88]. More studies have been focused on the latter [89].

In this regard, Kayed and Lasagna-Reeves [90] have demonstrated that after being incorporated into the membrane, Aβ undergoes conformational changes which is much more prone to aggregation on

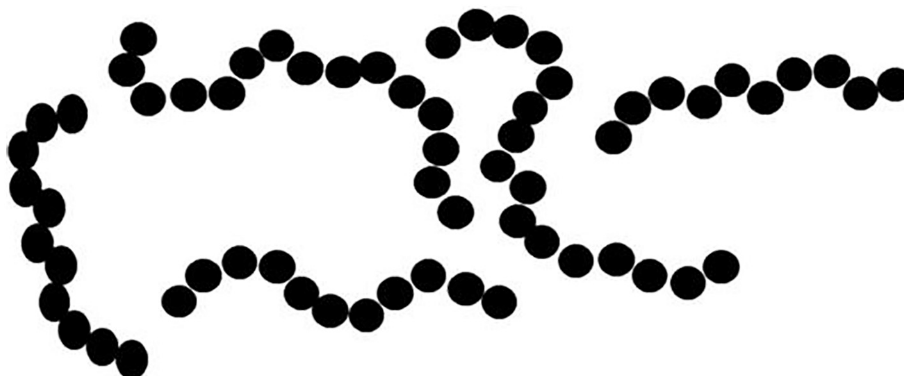

Fig. 2. The schematic diagram of protofibils.

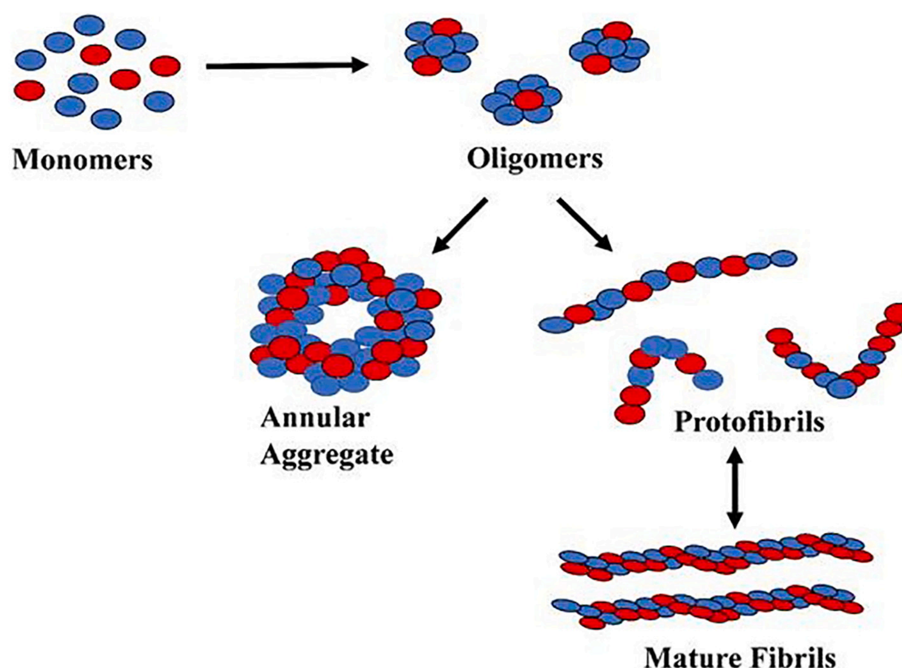

Fig. 3. The pathway of fibril formation.

the membranes, and which ultimately leads to toxicity of the cell. These authors also suggested the possibility that the changes in the ratio of cholesterol to phospholipids in the membrane alters membrane fluidity, and thereby favours aggregation of Aβ. Furthermore, the presence of rafts on the membrane may also influence aggregation of Aβ [91].

These data, along with other reports, have led to "channel hypothesis", which suggests that amyloid peptide channels are involved in ion deregulation leading to manifestation of degenerative disease [92,93]. Once Aβ channels are formed on the neuronal membrane, disruption of calcium and other-ion homeostasis may take place, resulting in the promotion of numerous degenerative processes, including free radical formation [94], and phosphorylation of tau [95], thus accelerating neurodegeneration. Interestingly, free radicals are also capable of inducing membrane disruption; consequently, the unregulated calcium influx is amplified. The disruption of calcium homeostasis influences the production and processing of APP (amyloid precursor protein). Thus, a vicious cycle of neurodegeneration is initiated [96].

Contrary to the amyloid channel hypothesis, recent data suggest that homogeneous solutions of amyloid oligomers increased the conductance of artificial lipid bilayers that did not show channel-like properties. These oligomers enhanced ion mobility across the lipid bilayer [97]. Accumulating evidence suggests that membrane permeabilization by amyloid oligomers is a common mechanism of pathogenesis that plays an important role in amyloid-related degenerative diseases [98–111]. Interestingly, studies have also demonstrated that membrane permeability caused by amyloid oligomers occurs due to the defects in the lipid bilayer, rather than formation of discrete proteinaceous pores.

Consistent with these observations, Demuro et al. [97,101] have shown that amyloid oligomers result in increased Ca^{2+} levels, whereas equivalent concentrations of monomers or fibrils did not [102]. These amyloid oligomers disrupt both plasma and intracellular membranes in a channel-independent manner. The authors proposed that amyloid oligomers increased the permeability of the plasma membrane and thereby penetrate the cells, and consequently disrupt intracellular membranes leading to leakage of sequestered Ca^{2+} [112]. Furthermore, Kayed et al. [96] have reported that soluble oligomers are formed from several different types of amyloid which specifically increased the lipid bilayer conductance regardless of the protein sequence, whereas fibrils and soluble low molecular weight species of Aβ had no effect. In fact, the increase in membrane conductance occurred without any evidence of discrete ion channel or pore formation or ion selectivity [97]. In a similar vein, oligomeric forms of amyloidogenic proteins cause disruption in synaptic activity and plasticity before cellular degeneration. Synaptic dysfunction, rather than neuron loss, may be the cause of motor impairment and memory loss early in neurodegenerative disease progression [113].

Another mechanism by which extracellular Aβ oligomers cause toxicity to neuron cells is by binding to the cell-surface receptors such as the *N*-methyl-D-aspartate receptor (NMDAR) [114] and other receptors which culminate into synaptic dysfunction and neurodegeneration. In particular, Yamamoto and group [115] have shown that Aβ oligomers induce nerve growth factor (NGF) receptor-mediated neuronal death. Other reports on neuronal receptor-mediated toxicity mechanisms indicate that Aβ disturbs NMDAR-dependent long-term potentiation induction both in vivo and in vitro. Furthermore, Aβ specifically inhibits several major signaling pathways downstream of NMDAR, including the Ca^{2+}dependent protein phosphatase calcineurin, Ca^{2+}/calmodulin dependent protein kinase II (CaMKII), protein phosphatase 1, and cAMP response element-binding protein (CREB) [116].

In addition to their accumulation extracellularly, a large body of evidence indicates Aβ oligomers accumulate intracellularly [117–119]. Accumulated intraneuronal Aβ oligomers have also been identified in the brain of AD patients, transgenic mice, and cultured cells [120–126]. Moreover, it has been found that intraneuronal Aβ accumulation appears prior to extracellular amyloid plaque formation, and this results in synaptic dysfunction [120–129]. Almeida et al. [130] have demonstrated that, in Aβ mutant transgenic mice and human AD brain, Aβ accumulates in intraneuronal bodies, especially in multivesicular bodies (MVBs) [130]. These authors also noted that Aβ accumulation in neurons inhibits the activities of the proteasome and deubiquitinating enzymes. Thus, in AD, Aβ accumulation in neurons impairs the MVB sorting pathway via the ubiquitin-proteasome system (UPS). Therefore, this leads to inhibition of the proteasome, resulting in an increase in Aβ oligomer levels and consequently causing AD [131,132].

In the human cell model, Aβ interacted with α-subunit of proteasome and sequestered into aggregates. Furthermore, in vivo mouse model overexpressing Aβ oligomers and administration of anti Aβ-antibody results in a reduction of oligomer levels in the brain, while

simultaneously increasing proteasome activity [62].

Another major pathway through which neuronal proteins remove or degrade cellular components and cause neurodegenerative diseases is autophagy, where waste proteins are sequestered in a vacuole containing different hydrolytic enzymes capable of degrading these cellular proteins and other cellular systems. Recent studies indicate that Beclin-1 initiates the autophagy pathway by initiating the formation of phagosomes through recruitment of other proteins. However, if Beclin interacts with bcl-2, it prevents autophagosome formation and leads to apoptosis and neural death. Interestingly, the Aβ monomer inhibits this interaction, while the amyloid oligomer increases the formation of Beclin-1:bcl-2 complexes and eventually causes neuronal death [133].

Oxidative stress is another mechanism by which the Aβ oligomer causes toxicity. Oxidative stress is mainly characterized by protein, DNA and RNA oxidation, and lipid peroxidation [134,135]. Patients with AD showed an increase in oxidative stress. Oxidative stress may induce overproduction of Aβ peptides by activating β-secretase [136]. These overproduced Aβ peptides may aggregate into toxic oligomers leading to initiation of the free radical process. This results in a vicious cycle causing new oxidative stress, accompanied with increased macroautophagy by lysosome, resulting in apoptosis [137].

3. Parkinson's disease (PD)

PD involves a complex, multisystem brain degeneration primarily associated with dopaminergic neurons located in the substantia nigra (SN) of pars compacta, and manifests itself in the form of motor impairment followed by cognitive loss and dementia. This loss of neurons has been reported to be caused by the presence of aggregates (Lewy bodies) and neurites (LNs), the major constituents being the fragments of the protein, α-synuclein. PD is also characterized by depletion of dopamine in the brain [138,139]. It has been proposed that AD neuropathology (misfolded Aβ) may influence PD progression by acting synergistically with α-synucleinopathy and vice-versa. Contrarily, in an interestingly anomalous report, a research group ruled out any association of Aβ deposition with cognitive impairment in PD [140]. They investigated the extent of the affected misfolded Aβ deposition (AD pathology) on PD (cognitive deficit and dementia), but failed to find an association between amyloid deposition and cognitive impairment in a moderately large sample, enriched with PD patients at risk of dementia.

A direct evidence of involvement of α-synuclein in the neurodegenerative processes in PD comes from genetic studies. Autosomal dominant early-onset Parkinson's disease occurs only in a small number of families. The three different missense mutations occur in the α-synuclein gene, including A30P, E46K, and A53T [141–143]. The production of wild type α-synuclein in transgenic mice [144] or of WT, A30P, and A53T in transgenic [145], led to motor deficits and neuronal inclusions, which bears resemblance to PD. Cells transfected with α-synuclein develop LB-like inclusions. Numerous studies from different laboratories have established that recombinant α-synuclein easily assembles into amyloid-like fibrils in vitro and this process is modulated by familial point mutations. Based on these observations it is clear that PD is a syncleinopathy; i.e., a neurode-degenerative disease whose pathogenesis is linked to α-synuclein aggregation[1–3,146–154].

All of these three PD-related point mutations, A30P, E49K, and A53T have been shown to accelerate the α-synuclein aggregation (but not fibrillation) in vitro. Conformational studies of wild-type and point mutation of α-synuclein are now available. Detailed conformational analysis showed that (wild type) α-synuclein and A30P and A53T mutants possess similar conformations [155], suggesting that mutations do not affect the overall structure of human α-synuclein, which remains in a natively unfolded state. This was further validated by WT α-synuclein, A30P, and A53T mutant studies, which showed that these proteins adopt a partially folded conformation, whose structure was shown to be independent of the mutations. Both mutations have been shown to reduce hydrophobicity in the vicinity of the substitution.

Consequently, the propensity to form α-helical structure was shown to be somewhat diminished in the N-terminal region of both mutants, whereas the pre-disposition to form β-structure was predicted to be slightly enhanced. However, the increased propensity to form β-sheets in these two mutants may not be strong enough to alter the overall structure of monomeric proteins, but may affect the aggregation behavior of α-synuclein mutants through specific stabilization of an intermolecular β-structure. High-resolution solution NMR structure revealed that the A30P mutation disrupts the helical structure [156], whereas the A53T mutation results in a slight enhancement preference for an extended conformation in a small region around the mutation site [157].

The effect of E46K mutation on aggregation of α-synuclein has been recently analyzed [155]. It has been established that the E46K mutation is also able to increases the propensity of α-synuclein to fibrillate, but this effect was less pronounced than that of the A53T mutation [155]. The E46K mutation is located in the fourth KTKEGV-type repeat in the amino-terminal region of α-synuclein. It has been emphasized that a Glu residue similar to Glu46 is present in 5 of the 7 degenerative repeats in α-synuclein, and the only repeat that does not have such a residue is repeat 2, which has Glu residues adjacent to each side of the repeat. Based on these observations it has been suggested that the N-terminal region of α-synuclein and, more specifically, Glu residues in the repeats, may be important in regulating the ability of α-synuclein to polymerize into amyloid fibrils. Theoretically, Glu and Lysine are beta sheet breakers. The mutant undergoes a change in charge. This implies that the microenvironment around mutant residue K46 is more favorable for aggregation reaction, and beta sheet propensity does not play a determining role in aggregation reaction.

Amyloid-β (Aβ) is also associated with PD and especially deposition of Aβ is associated with PD. According to some evidence low cerebrospinal fluid (CSF) $Aβ_{42}$ is predictive of future cognitive impairment in PD. It is the second most common neurodegenerative disorder and is characterized by progressive motor and cognitive impairments. Molecular imaging has confirmed the detection of pathological accumulations of Aβ-amyloid plaques. These plaques also have been confirmed by PET imaging. Amyloid plaques are also demonstrated in Parkinson's disease with dementia [158–162].

3.1. *Fibril structures of α-synuclein*

Recently, several atomic resolution structures of the fibrillar forms of α-synuclein have been solved. In 2016 Tuttle et al. [163] were the first to use ssNMR approach to solve the structure of α-synuclein at 4.8 Å resolution. More recently, in 2018 Guerrero et al. [164], using cryoEM, obtained a 3.4 Å resolution structure of synuclein. This was closely followed by a 3.1 Å resolution structure of α-synuclein obtained by Li et al. [165]. Interestingly, all of these three groups deduced the same 'Greek key' conformation independently, which is strikingly similar. Analyses of the structures showed that each αS subunit in the fibril adopts a β-sheet rich conformation, which is hydrogen bonded to other similar subunits spaced at 4.8–4.9 Å. The β-sheet rich structures lies in center regions between residues 42–102 and forms an inner hydrophobic core that interlocks into right-angled spirals.

The N-terminal residues 1–41 and C-terminal residues 103–121 are highly flexible coils and were therefore poorly resolved in ssNMR and CryoEM techniques. Upon further inspection of the structures of α-synuclein, it was found that hydrophilic amino acids are present on the surface, with the exception containing a few scattered hydrophobic amino acids: L38/V40 and F94/V95, with V82. The central region mainly comprises hydrophobic amino acid Ala/Val residues, and one Ile. The hydrophobic region lies inside the core of the protein molecule. In all of the three structures, a salt bridge between E46 and K80 occurs which further stabilizes the conformation of α-synuclein.

Although both cryoEM structures exhibited many common features, the most notable observation in this regard is that the fibrils are 10 nm wide and are composed of two adjacent protofilaments. These

protofilaments interact to form a hydrophobic steric zipper, with a salt bridge being formed between E57 and H50 of the adjacent subunits. In contrast, the structure determined by ssNMR generated single strand fibrils with a width of 5 nm. A striking feature is that the fibril polymorph interface is composed of small shallow hydrophobic residues (G51, A53, and V55) that are flanked by electrostatic interactions (K45/H50 → E57). The β-sheet structure of each subunit is further stabilized by two more electrostatic interactions K58 → E61 and E46 → K80. Importantly, these electrostatic contacts are buried within the fibril core, potentially enhancing their energetic contribution to overall fibril stability. Most of the Parkinson's disease mutations lie at the interface of these two subunits, suggesting their association in fibril formation and stability [18,11,59].

3.2. Structure of the α-synuclein oligomer

Oligomers of α-synuclein are similar to those of other amyloidogenic proteins, and are structurally highly diverse. Some of these are β-sheet rich, while others are primarily disordered. Recent studies identified several distinct populations of α-synuclein oligomers and obtained their structural information. For example, Giehm et al. discovered wreath-like oligomers with a diameter of approximately 18 nm [166]. These oligomers were able to disrupt the membranes and easily assemble into fibrils. Hong et al. identified the oligomers that are formed in parallel with fibril formation [167]. Their morphology depended on the salt concentration of the solution. These oligomers transformed into fibrils but disrupted the lipid membranes. Apetri et al. found that oligomers formed at the early stages of α-synuclein aggregation have a helical conformation [168]. Annular aggregates of α-synuclein have also been observed.

3.3. Mechanisms of α-synuclein toxicity

There are two important questions regarding α-synuclein aggregation in PD: which species is present during the aggregation of α-synuclein that could be responsible for neuronal death, and whether neurotoxicity can be ascribed to a single aggregate type? Toxicity may be exerted by specific populations of α-synuclein aggregates directly and/or be mediated via various routes through proteins involved in different cellular processes [169–171]. The mechanisms proposed to describe the neurotoxicity of α-synuclein and its aggregates can be grouped into three major classes: mechanical disruption of cellular compartments/processes, toxic gain of function, and toxic loss of function.

3.4. Mechanical disruption of cellular compartments/processes

One of the most commonly accepted examples of the mechanical disruption of cellular compartments/processes is permeation of cellular membranes by amyloid aggregates. α-Synuclein oligomers can bind to lipid membranes and disrupt membrane bilayers [172,173]. Certain oligomeric forms of α-synuclein were shown to penetrate membranes, forming pore-like channels [174]. Membrane permeation by amyloid oligomers without pore formation has also been proposed [175]. It is believed that this is one of the main mechanisms of toxicity for protein aggregates. Alternatively, impairment of α-synuclein degradation via proteasome inhibition by the aggregated species and copper-dependent generation of ROS have been proposed as possible mechanisms for neurotoxicity of α-synuclein aggregates [176].

3.5. Toxic gain of function of α-synuclein

With normal aging, the protein is concentrated in the cell body, and when coupled with post-translational modifications (i.e. phosphorylation, nitration, or truncation), or enhanced expression due to genetic multiplications or promoter polymorphisms, or with mutations that increase the stability of oligomers and decrease the stability of tetramers, the likelihood of fibril formation increases and eventually it forms insoluble inclusions. A gain of toxic function occurs when these insoluble inclusions cause neuronal and synaptic damage.

3.6. Toxic loss of function of α-synuclein

The sequestration of α-synuclein into these inclusions will bring the concentration of free soluble α-synuclein at the synapse below which is required for proper cellular functions. As a consequence, neuron dysfunction occurs, leading to neuron death and clinical and neuropathological manifestations of PD appearing. Consequently, α-synuclein-related pathology and aggregation represents a de facto loss-of function mechanism of toxicity [177,178]. This is further compounded by the fact that α-synuclein inclusions appear in the somata of neurons, indicating that the aggregates also remove α-synuclein from its normal subcellular compartment (i.e. the synapse). Thus, the synuclein is redistributed and accumulates during the normal aging process [179].

3.7. Other mutant genes are also associated with Parkinson's disease

Single gene mutations in the genes encoding α-synuclein (SNCA), ubiquitin C-terminal hydrolase like 1 (UCH-L1), parkin (PRKN), LRRK 2, PINK 1, and DJ-1 have also been reported to be associated with PD [180–182]. However, with the exception of LRRK 2, these single gene defects contribute to only a small number of patients with PD [183].

Interestingly, it has been reported that mutations in the gene glucocerebrosidase (GBA1) account for the most common genetic risk factor for sporadic PD and Dementia with Lewy bodies (DLB). They are particularly linked to cognitive deterioration. DLB is a classical alpha-synucleinopathy but s also frequently accompanied with additional AD pathology with amyloid-beta and Tau deposition. DLB patients manifest variable pathologies involving alpha-synuclein, amyloid-beta, and Tau [184–186], while PD patients with GBA1 mutations report lowered cerebrospinal fluid (CSF) levels of total alpha-synuclein. In their study, Lerche et al. [186] screened the GBA1 gene and single-nucleotide polymorphisms in SNCA rs356220, APOE rs429358, and MAPT rs1052587. In addition, they also screened the CSF levels of total alpha-synuclein, amyloid-beta1-42, total-Tau, phospho-Tau, and neurofilament light chain. The study was carried out with 100 patients of DLB and 39 controls. The severity of GBA1 mutations was found to be associated with the onset and higher prevalence of rapid eye movement sleep behavior disorder at a younger age. CSF levels of total α-synuclein were reported to be of the order $DLB_{GBApathogenic} < DLB_{GBAmild} < DLB_{GBA\text{-}wildtype}$. The pathogenic GBA1 mutations could thus possibly be associated with CSF α-synuclein profiles in DLB, as in PD. Interestingly, histopathological studies from PD_{GBA} reveal more diffuse neocortical Lewy body–type pathology compared to PD patients without mutation.

In juvenile cases, mutations in the parkin protein result in Parkinsonian syndrome (without Lewy bodies), suggestive of the major role of parkin protein in the growth of the Lewy bodies [187]. Furthermore, it has been found that parkin facilitates ubiquitination of proteins such as synphilin-1 (α-synuclein interacting protein) leading to the formation of Lewy bodies [188]. The LRRK 2 gene (PARK8) has been reported to be the most common cause of familial or sporadic PD. The frequency of LRRK2 mutations in patients with a family history of PD is 5–7% [7,203]. Many of the LRRK2 patients reported having typical features of PD with onset in middle or late age. In addition, genetic aberrations in the mitochondria is also very much associated with the PD pathology. Mutations in the Complex 1 of the oxidative phosphorylation pathways reported in PD brains suggest that the cells of the pars compacta are susceptible to oxidative damage [189,190]. This is elaborated on in the subsequent section.

4. The role of amyloid in mitochondrial dysfunction leading to neurodegeneration

As is very well known, the mitochondria are crucial multifunctional organelles that play numerous vital functions in the cell. They are not only the source of energy but also contribute to maintaining calcium homeostasis and many vital cellular metabolites as well as redox [191]. Neurons have a lifespan similar to that of the whole organism and are more sensitive to the accumulation of oxidative damages/accumulating defective mitochondria during the aging process compared to dividing cells [192]. Since all the neurodegenerative disorders are associated with the accumulation of abnormally aggregated misfolded proteins, they contribute to inhibiting mitochondrial function and inducing oxidative stress.

Mitochondrial dysfunction has an important role to play in contributing/aggravating various neurological conditions including AD and PD and vice versa. It originates/arises from various factors such as mitochondrial DNA damage, oxidative stress from reactive oxygen species (ROS), membrane and ionic gradient destabilization, and interaction with toxic proteins such as amyloid beta (Aβ). Several aspects of mitochondrial dynamics are altered in the neurodegenerative diseases, contributing to disease etiology and its manifestation. Many of the genes associated with PD or ALS are linked to mitochondria. Mitochondrial dysfunction may also be triggered by environmental toxins such as pesticides, food preservatives, and others. It is therefore crucial to investigate and understand the fundamental mechanisms, as well as all other possible factors involved in the pathological process of the disease, including mitochondrial dysfunction. This would possibly increase the chances for finding the best ways towards working for neuronal survival and effective neuroprotective therapies.

AD is characterized by the deposition of senile plaques caused by the extracellular deposition of the peptide Aβ and presence of intracellular tau neurofibrillary tangles (NFT). This aberrant aggregation of proteins results in many neuronal dysfunctions, including mitochondrial function, synaptic signaling, neuroinflammation, and neuronal loss [193]. Aβ plaques have been reported to deplete Ca^{2+} ions storage in the ER, which leads to an excessive cytosolic Ca^{2+}, further reducing the endogenous GSH levels and causing ROS accumulation [194]. ROS-induced oxidative stress is crucial in aggravating the AD pathology, causing further accumulation and deposition of Aβ peptides and vice versa [195]. The aggregates reduce mitochondrial respiration in neurons and astrocytes via the inhibition of complexes I and IV, thus causing ROS production [196].

A study reported that mitochondria isolated from neurons and incubated with Aβ peptides caused a fivefold increase in the rate of H_2O_2 production [197]. AD has also been related to voltage-dependent anion channel 1 (VDAC1) [198]. VDAC is present in the outer mitochondrial membrane and regulates vital functions such as Ca^{2+} homeostasis, oxidative stress, and mitochondrion-mediated apoptosis. Interestingly, VDAC1 levels increase in AD brains and its inhibition has been proposed as a novel target towards reducing cell death. Mitochondria are highly abundant in synapsis because of their on-site energy provision and calcium modulation [199].

The association of PD and mitochondrial dysfunctions has been established for a considerable time now. The age-related deteriorations in the mitochondria, as well as damage/mutations in the mtDNA, are linked with the increased risk for PD [200]. α-Synuclein has been reported to target mitochondria and hamper its functional activities [200–204]. The transition of this protein from its functional monomeric to toxic oligomeric structure alters its functional consequences in a number of ways, particularly in PD. Also, the involvement of the mitochondria in PD becomes evident from the presence of PD-related genes including PARK2, PINK1, DJ-1, and LRRK2, which regulate mitochondrial and ROS homeostasis [205–208]. PINK1 deficiency causes inhibition of complex I and results in impaired respiration and increased complex II [209]. Mutations in PINK1 gene cause a recessive form of familial PD [210,211]. Also, mitochondrial ROS production in familial and sporadic forms of PD has been reported to cause DNA damage and activate the PARP enzyme-associated DNA repair mechanism [212]. Oligomeric α-synuclein may also cause ROS production affecting mitochondrial function and inducing lipid peroxidation [213].

A recent study reports that α-synuclein oligomers interact with the ATP synthase and open the permeability transition pore in PD by inducing selective oxidation of the ATP synthase beta subunit and mitochondrial lipid peroxidation [214]. This triggers mitochondrial swelling, and ultimately cell death. Inhibition of oligomer-induced oxidation prevents the pore opening and hence all the associated pathologies. Ca^{2+} overload-induced mitochondrial damage also leads to the pore opening and may cause selective degeneration of nigrostriatal dopaminergic neurons in PD [215]. Genetic ablation of cyclophilin D, a mitochondrial matrix protein, has been shown to increase Ca^{2+} threshold of the permeability transition pore in vitro and counteract in vivo cell death in various disease models [216].

Drugs such as glutamate inhibitors/cholinesterase improve synaptic neurotransmitters, but mitochondrial dysfunction still remains a challenge [217]. Lately, the antioxidants loaded lipophilic phosphonium cation have been reported to enhance targeted activity to neuronal mitochondria [218–220]. Mitochondrial targets including MitoQ, MitoPBN, MCAT, MitoTempo, and MitoVitE concentrate within the mitochondria and scavenge free-radicals combating mitochondrial dysfunction. Szeto-Schiller (SS) peptides (which target the stability of the inner mitochondrial membrane) and DDQ molecules (which improve bioenergetics) reduce mitochondrial fragmentation [221–222].

5. Future prospect

Improved characterization of the structural species of amyloid assemblies in various neurodegenerative diseases and their correlations between structural characteristics and disease phenotype would play a major impact on our understanding of pathogenesis and, on the development of appropriate diagnostic and therapeutic. The several oligomeric species and associated neurotoxicity determines the pathogenicity and have an important role in biomarkers development and drug development. Developing therapeutics based on the differences in various multimeric species will be a far fetch approach, as they tend to recognize more than one species. Understanding the amyloid problem in the context of its environment, either their interaction with lipid raft or other proteins would be required at molecular and pathological level.

Acknowledgements

Authors acknowledge the facilities of Distributed Information Sub-Centre, Interdisciplinary Biotechnology Unit, A.M.U Aligarh.

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