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Antimicrobial Properties of Amyloid Peptides

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Abstract

More than two dozen clinical syndromes known as amyloid diseases are characterized by the buildup of extended insoluble fibrillar deposits in tissues. These amorphous Congo red staining deposits known as amyloids exhibit a characteristic green birefringence and cross-β structure. Substantial evidence implicates oligomeric intermediates of amyloids as toxic species in the pathogenesis of these chronic disease states. A growing body of data has suggested that these toxic species form ion channels in cellular membranes causing disruption of calcium homeostasis, membrane depolarization, energy drainage, and in some cases apoptosis. Amyloid peptide channels exhibit a number of common biological properties including the universal U-shape *β-strand-turn-β-strand* structure, irreversible and spontaneous insertion into membranes, production of large heterogeneous single-channel conductances, relatively poor ion selectivity, inhibition by Congo red, and channel blockade by zinc. Recent evidence has suggested that increased amounts of amyloids are not only toxic to its host target cells but also possess antimicrobial activity. Furthermore, at least one human antimicrobial peptide, protegrin-1, which kills microbes by a channel-forming mechanism, has been shown to possess the ability to form extended amyloid fibrils very similar to those of classic disease-forming amyloids. In this paper, we will review the reported antimicrobial properties of amyloids and the implications of these discoveries for our understanding of amyloid structure and function.

Keywords

Amyloid ion channels; *β-strand-turn-β-strand* motif; cytotoxicity; antimicrobial activity

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INTRODUCTION

Amyloid fibrils were first missidentified as amorphous starch-like deposits that stained with iodine by light microscopy. Rudolph Virchow named them “amyloid” thinking that carbohydrate was their principal constituent.[1] Subsequent research showed that in addition to glycosaminoglycans, the amyloid deposits contained a single protein in a β-sheet conformation.[2] The application of Congo red and other dyes to these deposits produced a classic microscopic pattern including green birefringence under polarized light.[3,4] X-ray difraction studies exhibited a cross-β structure, and electron microscopic studies uncovered extended amyloid fibrils of variable width and often indeterminate length.[5,6] Dozens of pathological specimen from different clinical syndromes exhibit these identical staining properties, despite the fact that the proteins involved vary widely in structure, function and primary sequence.[7,8] Thus, the amyloid β-sheet structure appears to be a final common pathway of misfolding for pathologic proteins. A number of different factors can contribute to the formation of amyloid β-sheet structures including proteolysis, amino acid mutation, high concentration, acidic pH, binding to metals and interaction with lipid membranes. The molecular mechanisms by which amyloid peptides cause disease remain elusive. However, a substantial body of evidence has amassed to implicate channel formation as a common mechanism of action amongst these diverse peptides.[9-18] Although no enzymatic activity or specific receptor has ever been convincingly demonstrated for amyloid peptides in disease pathogenesis, over a dozen amyloid peptides have been shown capable of forming ion channels in planar lipid bilayers and cellular membranes (Table 1). Furthermore, channel formation has been correlated with calcium dysregulation and apoptosis and cytotoxicity of host target cells for a number of different amyloids. In addition, inhibition of channel formation through dyes such as Congo red or blockade of channels using zinc prevents cytotoxicity. Thus, the channel hypothesis has become a leading theory to explain the pathogenesis of Alzheimer's disease (AD) and other amyloidoses.

The killing of micro-organisms by channel-forming toxins was demonstrated more than 3 decades ago.[19] Subsequent work has shown that pore-forming toxins that kill micro-organisms are widespread in the prokaryotic and eukaryotic community.[20] It has also been shown that human host defense peptides such as defensins and protegrins kill invading microbes through a channel-forming mechanism.[21,22] A number of these peptides were also shown to exhibit a β-sheet structure similar to that possessed by amyloid peptides. Work by Thundimadathil and colleagues[23,24] has further shown that generic β-sheet peptides of appropriate length would spontaneously form channels in planar lipid bilayer membranes. Taken together, these various studies suggested a parallel between channel-forming amyloid peptides and channel-forming antimicrobial peptides (AMPs) based on a common β-sheet structure (Figure 1A and B). These parallels were strengthened by theoretical studies,[25] which showed that models of toxic β-sheet protegrin-1 (PG-1) channels have a subunit organization motif that was very similar to that of the Alzheimer's β-amyloid (Aβ) channels they had previously modeled (Figure 1C-J). These works suggested that the β-sheet played a critical role in predisposing peptides to interact with membranes and form channels. Indeed, structural studies had previously revealed that several important channel-forming toxins including staphylococcal α-toxin,[26] anthrax toxin,[27] and *Clostridium* perfringolysin O form large lumen β-sheet barrels in the membrane which caused a toxic leakage of cellular constituents.[28]

Two recent studies have sharpened the focus on the parallels between amyloids and antimicrobial peptides. In 2010, Soscia *et al.*[29] demonstrated that the Aβ peptide from AD possessed antimicrobial properties. They suggested that this might in fact be the *in vivo* function of Aβ. They specifically compared the antimicrobial activity of Aβ and LL37, a well-known human AMP. In 2011, Jang *et al.*[30] reported that the human antimicrobial PG-1

could form amyloid-like fibrils as demonstrated by atomic force microscopy and thioflavin T staining. These fibrils were morphologically similar to those of Aβ, and the authors suggested that this was further evidence that amyloid peptides *in vivo* could have an antimicrobial function. In the remainder of this paper, we will briefly review the properties of amyloid peptide channels and the antimicrobial effects of various amyloid peptides that have been reported so far. We will conclude with the consideration of the relationship between amyloid formation, β-sheet structure, channel formation, and antimicrobial and cytotoxic activity. These considerations have important implications for theories of the pathogenesis of amyloid disease and for development of novel antimicrobial agents.

AMYLOID PEPTIDE TOXICITY: THE OLIGOMERIC INTERMEDIATES

Amyloid is a pathologic diagnosis based on the binding of Congo red and other dyes to peptides in β-sheet conformation. The β-sheets of these peptides are able to stack in an extended manner resulting in the formation of elongated fibrils that become insoluble. Although these fibrils have been subjected to extensive biophysical characterization, there is now substantial evidence, which suggests that fibrils are not toxic to cells or tissues in general. Recent studies have strongly implicated smaller aggregates known as oligomers in cellular toxicity.[31,32] The mechanics and kinetics of amyloid oligomer formation are complex and beyond the scope of this review. However, it is important to note that the presence of lipid membranes has been implicated as a catalyst for oligomer formation.[33,34]

The amyloid cascade hypothesis[35] was stimulated by the findings that mutations in certain amyloids, particularly the Alzheimer's amyloid precursor protein (APP), were linked with clinical disease. It was also noted that these mutations tended to cluster around enzymatic cleavage sites of APP and thus might affect the production of the Aβ peptide. The demonstration of cytotoxicity of the Aβ peptide lent further strength to this theory.[36] Early on it was noted that monomers and fibrils showed little cellular toxicity but that intermediate-size aggregates called oligomers seemed to play a critical role in cytotoxicity.[31,32] This was soon followed by demonstration of cytotoxicity for amyloid oligomers from the prion protein and α-synuclein.[37,38] Interestingly, many of these early studies were plagued by the irreproducibility of amyloid peptide cytotoxicity. This was subsequently explained by Pike *et al.*[39] who demonstrated that the aggregation state of the Aβ peptide affected its cytotoxicity with monomers and fibrils showing little cytotoxicity but intermediate aggregation state presenting much higher cytotoxicity. The rapid, irreversible and unpredictable aggregation of amyloid peptides led to numerous problems with reproducibility of results even within labs. Further research demonstrated that the early stages of amyloid peptide aggregation were quite slow, but after a critical mass was achieved, the kinetics became much more rapid. It was also shown that addition of preformed seeds or nuclei to solutions of monomers could dramatically speed up the process of fibril aggregation. However, it was also observed that extended periods of aggregation into fibrils could lead to a decrease in cytotoxicity, and it was suggested that fibril formation might actually serve a protective function for the organism by sequestering the toxic smaller peptides in insoluble form. The sequestration of some of these amyloid fibril aggregates in membrane-bound inclusion bodies such as Lewy bodies supported the idea that fibril formation was cell protective. This was convincingly demonstrated in the inclusion bodies containing extended aggregated polyglutamine tracts in Huntington's disease.[40]

Transgenic mouse models of Alzheimer's and Huntington's disease were also consistent with the idea that oligomers rather than fibrils were toxic.[41] Behavioral learning and memory deficits in these transgenic mouse models would occur far earlier than the appearance of fibrils or inclusion bodies, thus indicating that the toxic effects of smaller aggregates on cellular function were happening prior to the production of amyloid fibrils.

THE β-SHEET CONFORMATION

The triggers for amyloid misfolding are diverse and well-established. The presence of metal ions, changes in pH or concentration, enzymatic cleavage or amino acid mutations have all been demonstrated to catalyze protein folding into β-sheet structure. More recently, it has been demonstrated that the presence of lipid bilayer membranes can also catalyze β-sheet formation.[42] β-sheet-rich peptides exhibit unique affinity for lipid bilayer membranes and are able to aggregate and orient themselves in the bilayer to optimize hydrophilic and hydrophobic interactions. The unfolding of a native protein also unleashes new hydrogen bonding possibilities.[43] These new possibilities for hydrogen bonding can provide a driving force for protein aggregation in addition to the hydrophobic effect. Together, these forces can drive self-aggregation. This is further aided by the ability of β-sheets to form intermolecular hydrogen bonds. These results suggest that the underlying physical chemistry of β-sheets predisposes this conformation to interact with lipid bilayers in a way that can lead to toxic ion channel formation (Figure 2). An alternative mechanism of membrane poration was proposed to involve the Aβ in an α-helical conformation, similar to the fusion domain of influenza hemagglutinin.[44] Further, α-synuclein has been reported to form a channel consisting of α-helices.[45]

AMYLOID PEPTIDE CHANNELS: ELECTROPHYSIOLOGY

Arispe *et al.*[9-12] first reported that the Aβ peptide could form ion-permeable channels in planar lipid bilayer membranes. This ground-breaking discovery was later extended to islet amyloid polypeptide (IAPP),[46] prion protein peptides,[47] and other amyloid peptides.[48,49] All of the reported amyloid peptide channels exhibited voltage independence and cation selectivity of a nonspecific type (Table 2). They all exhibited permeability to calcium thus providing a ready explanation for the disruption of calcium homeostasis that had been observed in numerous host target cells. The amyloid peptide channels exhibited multiple single channel conductances, unlike the homogeneous single channel conductances observed for the canonical channels of nerve and muscle cellular membranes. Their channel conductances were also much larger, and the heterogeneity of single channel conductances suggested that multiple molecular species might be forming channels in the membrane, similar to channel forming PG-1 AMP (Figure 3). The alteration of the single channel conductance distribution by treatments such as aging or acidic pH, which affected the aggregation state of the amyloid peptides, supported this notion. Extremely large channel conductances up to 5 nS, i.e. 1 to 3 orders of magnitude larger than conductances of conventional ion channels were reported,[9] and it was calculated that the leakage caused by such channels would cause rapid membrane depolarization and severe disruption of cellular energy stores. Channel formation by amyloid peptides was subsequently shown to occur not only *in vitro* but also in the cellular membranes of neurons, oocytes and fibroblasts.[50] The Aβ peptide was further shown to be capable of inhibiting long-term potentiation (LTP) in the hippocampus at nanomolar concentrations.[51] It was also shown that channel-forming variants of the Aβ peptide could inhibit LTP whereas nonchannel-forming variants could not. Walsh *et al.*[32] reported that naturally secreted Aβ oligomers were the sole species responsible for inhibition of LTP, thus demonstrating that this process could occur *in vivo*.

Channel formation by Aβ was subsequently demonstrated in rat cortical neurons[52,53] and in hNT cells,[54] and in small patches from gonadotropin-releasing, hormone-secreting neurons.[55] The properties of the channel *in vivo* and *in vitro* appeared to be indistinguishable. Diaz *et al.*[56] demonstrated that small molecule blockers of the Aβ channel could potently protect cells from Aβ toxicity, even at a relatively late stage. This group then went on to design highly specific blockers based on the hypothesized model of the pore region of the Aβ peptide. A strong boost to the channel hypothesis of AD was reported by

Liu *et al.*[57] who demonstrated that the potassium ATP channel activator, diazoxide, could improve memory and reduce Aβ and tau pathology in a transgenic AD mouse model. Diazoxide, a potassium channel opener, should hyperpolarize membranes and counteract the depolarizing effect of the Aβ peptide channel. This should reduce Aβ peptide toxicity and improve memory. Confirmation of this hypothesis was provided by Anekonda *et al.*[58] who demonstrated that blockage of voltage-dependent calcium channels could protect cultured neurons from Aβ toxicity. Structural modeling of the Aβ peptide has suggested that these peptides form highly mobile subunits, which can aggregate into large wide-lumen channel structures. Unlike classical ion channels, these structures are fluid and rearrange rapidly within the membrane.[59] These molecular dynamics (MD) models showed sizes and structures consistent with the multiple conductance states seen in electrophysiologic recording and the pore sizes in atomic force microscopy (AFM) and electron microscopy (EM) which demonstrated amyloid channels of outer diameter 8-10 nm and inner diameter of approximately 1-2 nm.[14] The convergence of these various biophysical methods on a common pore structure lent additional credence to the channel hypothesis.

ANTIMICROBIAL EFFECTS: β-AMYLOID PEPTIDE

Soscia *et al.*[29] reported antimicrobial properties of the Aβ peptide. They compared the antimicrobial activities of Aβ and LL37, which is a well-known human antimicrobial host defense peptide. They demonstrated antimicrobial activity in assays involving eight clinically relevant microorganisms. Aβ had a potency equivalent to or greater than LL37. They further demonstrated antimicrobial activity present in whole brain homogenates from patients with AD and that these activities were significantly higher than age matched controls without AD. The level of antimicrobial activity was proportional to the level of Aβ peptide in tissue. Aβ immunodepletion from the AD brain homogenates with Aβ antibodies reduced the antimicrobial activity of the brain homogenates. Pathogens that could be inhibited by Aβ peptide included *S. pneumoniae*, a leading cause of bacterial meningitis, and *Candida albicans*. They also suggested that Aβ might be one of a family of AMPs contributing to pro-inflammatory activities in AD. These authors pointed out that, at least one other disease, corneal amyloidosis, involves the deposition of an AMP in amyloid form. The antimicrobial protein, in this case, is lactoferrin, which accumulates in the subepithelium.[60,61] Furthermore, an amyloid pathology of the seminal vesicles of elderly men is also derived from an amyloid peptide, semenogelin.[62,63] The authors hypothesized that stimulation of the innate immune system could lead to the generation of Aβ and subsequent amyloid deposition. Alternatively, they considered that a CNS infection could lead to a self-perpetuating innate immune response. Previously others have proposed infectious etiologies for AD based on the presence of pathogen antibodies in higher numbers in AD victims.[64,65] These authors also note the strong parallels between AMPs and Aβ peptides. Both peptides associate actively with bilayers and are believed to exert their activity through channel formation.[13,14,16,32-36,66] They also note that mitochondrial depolarization in Alzheimer's, Parkinson's, and Huntington's is a common feature of amyloid disease and that mitochondria are believed to have originated as bacterial endosymbionts. The double membrane of mitochondria resembles the double membrane of bacteria structurally and functionally in that both membranes are actively polarized and can be depolarized by nonspecific channel formation.

OTHER EXAMPLES OF AMYLOIDS AND ANTIMICROBIAL PEPTIDES

Serum amyloid A

Hirakura et al.[67] reported channel formation by the acute phase reactant protein serum amyloid A (SAA). Serum amyloid is comprised of the family of related apolipoproteins associated with high density lipoprotein. During states of infection or inflammation, levels

of acute phase isoforms of SAA can rise up to 1000 fold in the serum, and N terminal fragments of SAA can assemble into amyloid fibrils which localize to spleen, liver, and kidney. The authors reported that an acute phase isoform variant of SAA could readily form ion channels in planar lipid bilayers. These channels possess physiologic properties similar to those of other amyloid peptide channels. The expression of this acute phase isoform peptide expressed in bacteria was reported to induce lysis of bacterial cells in contrast to expression of the constitutive isoform, which did not. Sequence examination of the N-terminal portion of the acute phase isoform indicated strong hydrophobicity, which could have been responsible for targeting the cell membrane. The authors postulated a role for SAA in host defense as an AMP.

Microcin E492

Microcins are low molecular weight bacterial toxins produced by gram-negative bacteria. Microcin E492 is a known pore-forming bacterial toxin produced by *Klebsiella pneumoniae RYC492*.[68] Its antimicrobial action is limited to related strains of Klebsiella. Although it does not cause any known amyloid disease, it was demonstrated to form amyloid-like fibrils reflecting a β-sheet structure.

Protegrin-1 (PG-1)

Jang *et al.*[30] demonstrated that the AMP PG-1 could form amyloid-like fibrils. They used AFM and thioflavin T staining to characterize fibrils and compare them to $A\beta_{1-42}$ fibrils. Their kinetics of fibril formation was rapid compared to $A\beta_{1-42}$. They further noted that the anionic lipid bilayers appeared to inhibit fibrillation of PG-1 and favor small oligomer formation. MD simulations confirmed the presence of small oligomers on the membrane bilayer. Protegrins belong to a class of basic host defense peptides rich in cysteine and adopting a β-sheet structure. They are remarkably small at only 18 residues, about half the size of the better known defensins. Protegrins possess toxic activity against bacteria, fungi, and viruses that are enveloped by cell membrane. Safely sequestered in the Azurophilic granules of neutrophils and macrophages, protegrins exist in an insoluble state, until their host cell involves an invading pathogen. The granules then fuse with the pathogen vacuole, and the protegrin activity is released. Channel formation has been demonstrated to be the mechanism of action of protegrins.[22,66] This mechanism appears to be common to a number of host defense peptides, including defensins[21] and cathelicidins.[69]

Temporins

Temporins are a family of amphipathic α-helical peptides with antimicrobial properties. These remarkably short peptides, consisting of only 10-14 residues, appear to have selective lipid-binding properties that enable them to discriminate between target and host cells.[70] They were also demonstrated to cause permeabilization of the target cell membrane, a process that involves acidic phospholipid-induced conformational changes, peptide aggregation, and the formation of toxic oligomers in the membrane. This is a sequence remarkably similar to that hypothesized for amyloid peptides. *In vitro*, the oligomers can be converted to amyloid-like fibers. Conversion to the amyloid state detoxifies the peptides. Sequence analysis of various temporins and other α-helical AMPs led to the identification of "conformational switches." These domains possess equal probabilities for adopting random coil α-helical and β-sheet structures. Thus, they were able to switch easily from one conformation to another.

Lysozyme

In addition to its known enzymatic activities, lysozyme has a well-defined antimicrobial activity. The antimicrobial activity is clearly associated with the ability to permeabilize cell

membranes, most likely through a channel formation mechanism. Lysozyme is also capable of forming amyloid fibers and deposits.[71]

Antimicrobial properties for several amyloid peptides are summarized in Table 3.

ARE ALL AMYLOIDS ANTIMICROBIAL?

The provocative suggestion that Aβ plays a functional role as a host defense peptide remains to be confirmed. Given the wide variety of amyloids with known functions in their native state, it seems unlikely that all of these peptides could be intended to misfold into host defense peptides. Nevertheless, it now seems likely that, for at least some of these amyloids, an antimicrobial function is intended. There is good evidence for this for serum amyloid A and microcin E492. There also seems to be evidence for this for the temporins, a family of amphipathic α-helical AMPs.[70] There are many other related AMPs whose ability to form amyloid has not yet been tested. Further experiments could confirm this link between the requirements for amyloid fibril formation and requirements for channel formation by host defense AMPs. The β-sheet structure seems to be the underlying physical chemical commonality relating these two functionalities. Intriguingly, there is also evidence that amyloid formation can be protective in disease states. Specifically, in the case of Huntington's disease, inclusion body formation is protective to Huntington's affected neurons. There is also evidence that Lewy body formation in Parkinson's disease is protective to dopaminergic neurons. More recently, Riek and colleagues[72] have made the remarkable discovery that peptide hormones in storage granules are arranged in an amyloid fibril-like state. This arrangement renders them insoluble and efficiently stored within a secretory granule and ready to be dispersed by granule exocytosis into the extracellular space. This has provided the strongest evidence to date that the amyloid state can have a positive physiologic role. Further evidence of a positive functional role for amyloid has come from the study of bacterial curli.[73] *E. coli* and other gram-negative enteric bacteria, produce extracellular amyloids, known as curli. These fibers appear to be critical for growth in biofilms. The curli also play a key role in binding to host cells and enabling bacteria to persist within their local environment. The amyloid-forming proteins from curli contain 5 glutamine asparagine-rich peptide repeats composed of roughly 20 amino acids. These peptides are predicted to form *β-strand-turn-β-strand* motifs that can stack perpendicular to the fibril axis. Further experimental evidence suggests that the growth of amyloid fibers is tightly regulated by one protein which is secreted and anchored to the outer membrane, where it forms a template. The second curli fiber protein then adds onto the first, in a nucleation process similar to the seeding seen with eukaryotic amyloid proteins. After a nucleus is formed, the growing fiber can become a template for additional monomers. The separation of nucleation from seeding ensures that amyloid fibers occur only at the appropriate location and at the appropriate developmental stage.

Another example of functional amyloid fibers are the chaplins.[74] These extracellular structures are produced by the gram-positive bacterium *Streptomyces coelicolor*. The functional role of these fibers is to reduce surface tension at the air-water interface and permit the growth of aerial hyphae. The chaplins are critical for this development and have been shown to assemble into β-sheet-containing insoluble fibers that strongly bind thioflavin T. The chaplin biogenesis process is regulated in both time and space and is localized to the extracellular space, most likely to limit exposure to cytotoxic intermediates.

CONCLUSIONS

The discovery of links between amyloid fiber formation and antimicrobial β-sheet peptides is important for our understanding of both amyloid pathology and antimicrobial activity. The

β-sheet structures common to both processes also appear to be critical in allowing peptides to insert into membranes and assemble into pore-forming structures. The molecular models of these structures are highly reminiscent of the β-barrel structures, which have been determined experimentally for several pore-forming toxins. This suggests that the β-sheet is a structure optimized for nonspecific pore formation. While the small highly selective and tightly regulated ion channels of nerve and muscle cells that mediate electrical excitability are dominated by α-helical structures, it appears to be the case that toxic channel-forming peptides rely more heavily on β-sheet structures. The toxic peptides do not require a high degree of ion selectivity or tight regulation by voltage or neurotransmitters. The relative nonselectivity and heterogenous structure of these ion channels is, in fact, what makes them so toxic and unpredictable and remain a major challenge to develop any specific pharmacologic inhibitors. The fact that toxic β-sheet ion channels are effective antimicrobial agents also suggests that the locus of amyloid cytotoxicity in eukaryotic cells may well be mitochondria. Mitochondrial membranes bear a strong resemblance to prokaryotic membranes, both structurally and functionally. It is also clear that depolarization of mitochondria and bacteria are functionally devastating. In several amyloid diseases, there is strong evidence suggesting that mitochondrial depolarization often leads to apoptosis and plays a key role in the pathogenesis of these diseases. Thus, a deeper understanding of the mechanism of action of antimicrobial peptides may also strengthen our understanding of the pathogenesis of amyloid diseases, such as Alzheimer's, Parkinson's, and Huntington's. The remarkable convergence of these two fields is likely to deepen and enrich our understanding of both. It also represents a difficult pharmacological challenge, since high specificity drugs aimed at inhibiting amyloid channels are conceptually and experimentally harder to achive for such a mobile and flexible structures than they are for well defined structures such as α helix rich channels.

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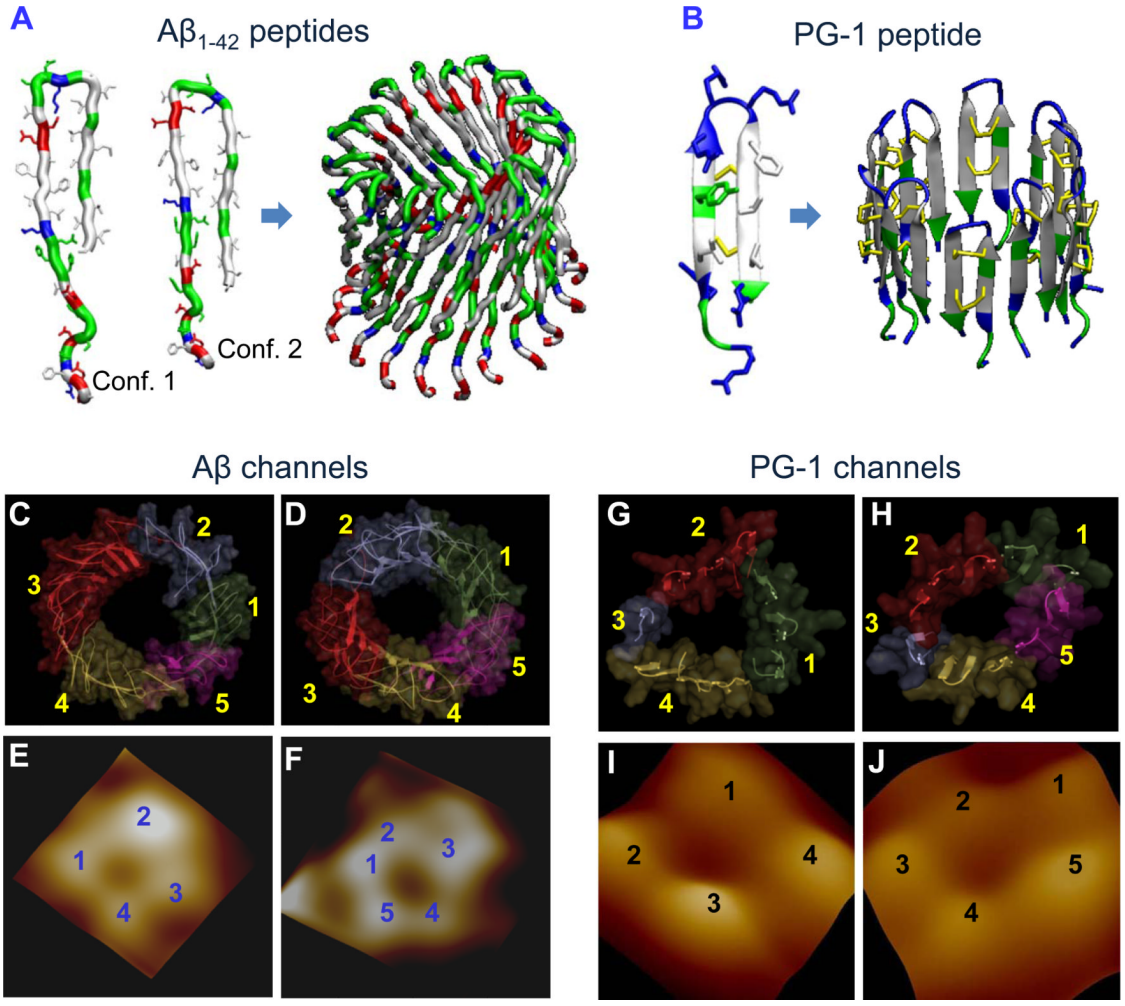

Figure 1.

(A) Monomer conformations of $A\beta_{1-42}$ peptides with different turn at Ser26-Ile31 (conformer 1) and at Asp23-Gly 29 (conformer 2), and the starting point of MD simulation for conformer 2. (B) Monomer conformation of 18-residues PG-1 peptide and the starting points of MD simulation. $A\beta_{1-42}$ peptides have the U-shaped *β-strand-turn-β-strand* motif, while PG-1 is a β-hairpin with two disulfide S-S bonds. In the cartoons, hydrophobic residues are shown in white, polar residues and Gly are shown in green, positively charged residues are shown in blue, and negatively charged residues are shown in red. In PG-1, disulfide bonds are highlighted in yellow. Side-by-side comparison between the (C-F) Aβ and (G-J) PG-1channels. The simulated Aβ barrel structures with highlighted subunits for the (C) $A\beta_{17-42}$ (p3) and (D) $A\beta_{9-42}$ (N9) barrels (Taken from Jang *et al.*[18]). All barrels are viewed from the top leaflet of the lipid bilayer and depicted in a cartoon representation with a transparent surface. Each subunit in the channels is colored in a different color. AFM imges of (E) p3 and (F) N9 channels show show four or five subunits, consistent with the simulated barrels (Taken from Jang *et al.*[17]). Image sizes are 15×15 and 23×23 nm^2, respectively. The simulated PG-1 channel structures with highlighted subunits for the (G) antiparallel and (H) parallel β-sheet channels of PG-1, and (I and J) AFM imges of PG-1 ion channels with different subunit organization (Taken from Capone *et al.*[66]). Permission for all reproduced figures will be obtained.

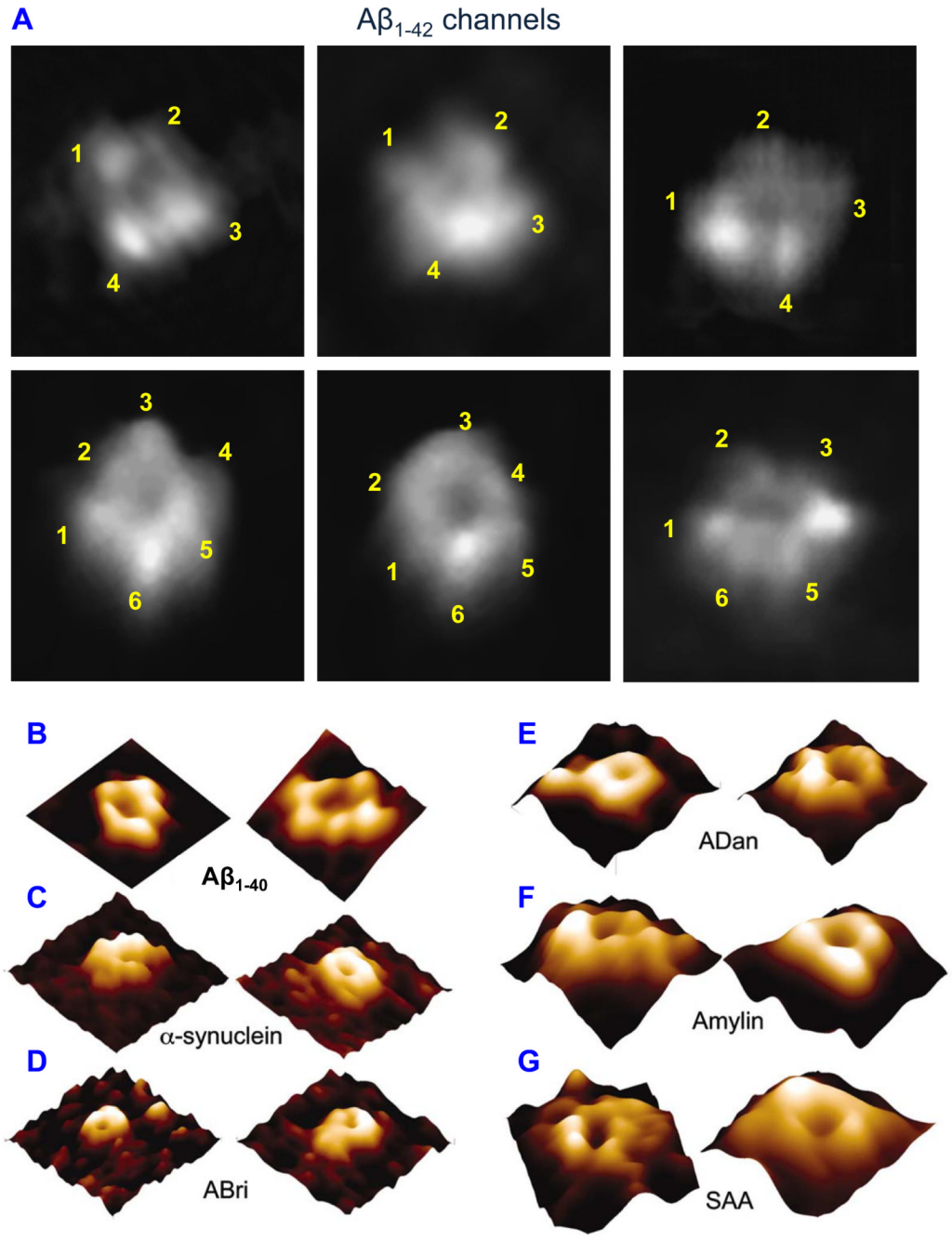

Figure 2.

AFM images (A) $A\beta_{1-42}$ (Taken from Lin *et al.*[13]), and (B) $A\beta_{1-40}$ and other various amyloid channels (Taken from Quist *et al.*[14]), including (C) α-synuclein, (D) ABri, (E) ADan, (F) Amylin, and (G) SAA. Permission for all reproduced figures will be obtained.

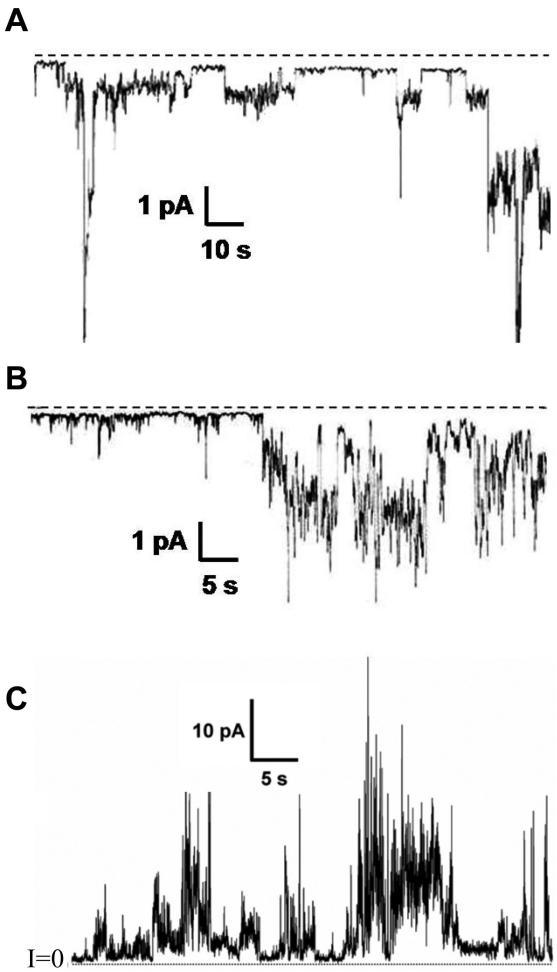

Figure 3.

Channel conductance measurements representing single channel currents induced by (A) $A\beta_{17-42}$ (p3) and (B) $A\beta_{9-42}$ (N9) channels (Taken from Jang *et al.*[17]), and (C) PG-1 channels (Taken from Capone *et al.*[66]). Permission for all reproduced figures will be obtained.

Table 1

Amyloid Diseases and Proteins

Disease	Protein	Abbreviation
Alzheimer's disease (AD), Down's Syndrome (Trisomy 21), Heredity cerebral angiopathy (Dutch)	Amyloid precursor protein (β-amyloid 1-42)	APP ($A\beta_{1-42}$)
Kuru, Gerstmann-Straussler-Scheinker Syndrome (GSS), Creutzfeld-Jacob disease, Scrapie (sheep), Bovine spongiform encephalopathy (“mad cow”)	Prion protein	PrP^{c}/PrP^{sc}
Type II diabetes mellitus (adult onset)	Islet amyloid polypeptide (amylin)	IAPP
Dialysis-associated amyloidosis	β-2-microglobulin	β2M
Senile cardiac amyloidosis	Atrial natriuretic factor	ANF
Familial amyloid polyneuropathy	Transthyretin	TTR
Reactive amyloidosis familial mediterranean fever	Serum amyloid A	SAA
Familial amyloid polyneuropathy (Finnish)	Gelsolin	Agel
Macroglobulinemia	Gamma-1 heavy chain	AH
Primary systemic amyloidoses	Ig-lambda, Ig-kappa	AL
Familial polyneuropathy - Iowa (Irish)	Apolipoprotein A1	ApoA1
Hereditary cerebral myopathy – Iceland	Cystatin C	Acys
Nonneuropathic hereditary amyloid with renal disease	Fibrinogen α	AFibA
Nonneuropathic hereditary amyloid with renal disease	Lysozyme	Alys
Familial British dementia	FBDP	A Bri
Familial Danish dementia	FDDP	A Dan
Diffuse lewy body disease, Parkinson's disease	α-synuclein	AS
Fronto-temporal dementia	tau	tau
Amyotrophic lateral sclerosis	Superoxide dismutase-1	SOD-1
Triplet-Repeat Diseases: (Huntington's, Spinocerebellar ataxias, etc.) Spinal & bulbar muscular atrophy Spinocerebellar ataxias Spinocerebellar ataxia 17	Polyglutamine tracts in the following proteins: *Huntingtin* Androgen receptor, Ataxins TATA box-binding protein	PG

Table 2

Channel Properties of Amyloid Peptides

Peptide	Single Channel Conductance	Ion Selectivity (Permeability ratio)	Blockade by Zinc	Blockade by Copper	Inhibition by Congo Red	Reference
$A\beta_{25-35}$	10-400 pS	Cation (P_K/P_{Cl}=1.6)	+	+	+	75,76
$A\beta_{1-40}$	10-2000 pS	Cation (P_K/P_{Cl}=1.8)	+			3
$A\beta_{1-40}$	50-4000 pS	Cation (P_K/P_{Cl}=11.1)	+			9,10
$A\beta_{1-42}$	10-2000 pS	Cation (P_K/P_{Cl}=1.8)	+		+	3
$A\beta_{1-40}$	Variable	Cation	+	+		77-80
$A\beta_{1-40/42}$	Variable	Cation	+			81
$A\beta_{17-42}$ (p3)	Variable	Cation	+			17
CT105 (C-terminal fragment of APP	120 pS	Cation	+		+	82
Islet amyloid polypeptide (Amylin)	7.5 pS	Cation (P_K/P_{Cl}=1.9)	+		+	46
PrP106-126	10-400 pS	Cation (P_K/P_{Cl}=2.5)	+		+	47
PrP106-126	140, 900, 1444 pS	Cation (P_K/P_{Cl} >10)	+	+		83
PrP82-146		Cation (variable)				84
PrP106-126 (deamidated)				+		85,86
Serum amyloid A	10-1000 pS	Cation (P_K/P_{Cl}=2.9)	+		+	67
C-type natriuretic peptide	21, 63 pS	Cation (P_K/P_{Cl}.>10)	+		+	87,88
β2-Microglobulin	0.5-120 pS	Non-selective	+		+	49
K3 fragment of β2M	Variable	Cation (P_K/P_{Cl}~ 5)	+			89
Transthyretin	Variable	Cation (variable)	+		+	90
Polyglutamine (AVG MW=6000)	19-220 pS	Non-selective	-		-	48
NAC (α-Synuclein 65-95)	10-300 pS	Variable	+		+	91
ABri	Variable	N.D.	+		+	14
ADan	Variable	N.D.	+		+	14

Table 3

Antimicrobial Properties of Amyloid Peptides

Peptide	Antibacterial	Antifungal	Antiviral	References
$A\beta_{1-42}$	+	+		Soscia *et al.* (2010)[29]
Serum Amyloid A	+			Hirakura *et al.* (2002)[67]
Microcin E492	+			Lorenzo (1984)[68]
Temporins	+	+		Mahalka & Kinnunen (2009)[70]
Protegrin-1 (PG-1)	+	+	+	Jang *et al.* (2011)[30,66]