CHAPTER 9.B

Structure of selected fragments of Aβ(1−42) in complex with other proteins

Mateusz Banach[1], **Irena Roterman**[1]
[1]Department of Bioinformatics and Telemedicine, Jagiellonian University−Medical College, Krakow, Poland

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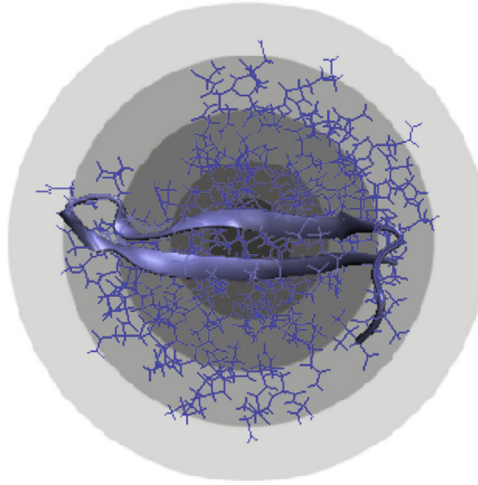

From Globular Proteins to Amyloids
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Visualization of the stable structure of Aβ(16−40) conditioned by a permanent chaperone (external protein)

In our search for ways to prevent the generation of amyloid fibrils we have identified various chemical factors, including ligands and scaffold molecules, capable of binding individual fragments of the Aβ(1−42) polypeptide (see chapter 9A).

Techniques discussed in this chapter include complexation of external proteins [1,2], inserting fragments of amyloid proteins into other proteins − in particular the V domain of the IgG light chain [3] and complexation with ligands [4,5]. According to the authors' intentions, all these factors should result in the base polypeptide adopting conformations which do not produce amyloid fibrils. Analysis of such "arrested" peptides is based on the fuzzy oil drop model, where we compare the structure of the observed hydrophobic core with the corresponding theoretical distribution of hydrophobicity in an ideal protein.

The model is not always applicable − for instance, it fails to produce correct results for very short polypeptides which do not have a tertiary conformation. Nevertheless, it enables us to carry out comparative analysis by facilitating quantitative description of diverse structural forms. As a result, we may identify structural properties which promote amyloidogenesis.

Non-amyloid conformations of Aβ(1−42) fragments

This chapter discusses different fragments of the Aβ(1−42) peptide which − when complexed with other proteins − do not adopt amyloid-like conformations. Such external proteins (or other stabilizing factors) effectively act as "permanent chaperones", since in their absence the Aβ(1−42) chain may instead produce an amyloid-like form. The definition of a chaperone highlights its role in preventing the accompanying polypeptide from misfolding. Chaperones perform their function by temporarily disallowing specific structural rearrangements. The concept of a "permanent chaperone" builds upon this definition by removing temporal restrictions and assuming that the chaperone must be present at all times, as long as the protein performs its function. This property characterizes all structures discussed in this chapter.

The following proteins are discussed below:

1. Aβ(17−27) (PDB ID: 4MVL) − "packaged" with lipocain [1].
2. Aβ(16−28) (PDB ID: 4MVI) − in complex with lipocain [1].
3. Aβ(16−40) (2OTK) − "packaged" with a synthetic protein [2].

4. Aβ(16—28) (PDB ID: 2M9R and 2M9S) — in complex with the Y23 ligand *(2s,3s)-3-(3,5-Dihydroxyphenyl)-2-(4-Hydroxyphenyl)-4- [(E)-2-(4-Hydroxyphenyl)ethenyl]-2,3-Dihydro-1- Benzofuran-6-Yl beta-D-Glucopyranoside [Polyphenol epsilon-Viniferin glucoside]*, also referred to as polyphenol ε-viniferin glucoside (EVG) [3].
5. Aβ(1—21) (PDB ID: 5HOX) — in complex with the JEF ligand — *O-(O-(2-Aminopropyl)-O'-(2-Methoxyethyl)polypropylene glycol 500) [Jeffamine]* [4]
6. Aβ(18—41) (PDB ID: 3MOQ) — fragment incorporated into the IgG V domain (hypervariable loop at 88—111 — position in V domain chain) [5].

Aβ(17—27) and Aβ(16—28) in complex with lipocain

Lipocain, a versatile protein, has been used to bind fragments (17—27) and (16—28) of the Aβ(1—42) polypeptide, rendering it soluble. It is expected that such fragments may appear at early stages of degradation of large integral membrane proteins, potentially leading to formation of amyloid fibrils. β-secretase and γ-secretase activity results in production of lipophilic Aβ peptides with a total length of 42 or 40 residues (fragments at 672—711/713). The authors hypothesize that the resulting peptides may be "arrested" using lipocain.

Our analysis concerns two complexes, involving Aβ(17—27) and Aβ(18—28) respectively (Fig. 9.B.1). Chain A is contributed by lipocain, while chain B represents the target peptide (13 aa — 4MVI and 11 aa — 4MVL) [1]. Table 9.B.1 illustrates FOD parameters for the entire complex

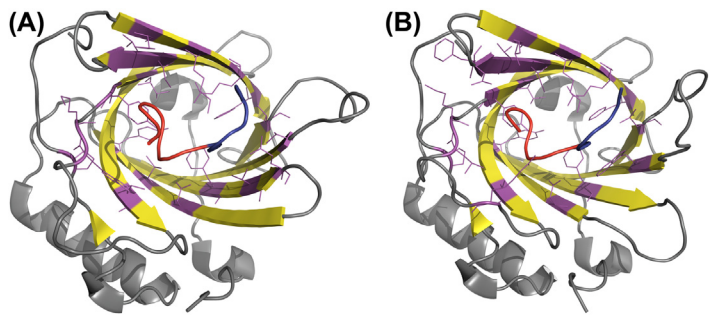

Fig.9.B.1 3D presentation of 4MVI and 4MLV complexes. (A) 4MVI chain A in complex with Aβ(16—28) peptide (chain B). (B) 4MVL chain A in complex with Aβ(17—27) peptide (chain E).Fragments 16—22 in Aβ(16—28) and 17—22 in Aβ(17—27) are shown in red. Fragments 22—28 in Aβ(16—28) and 22—27 in Aβ(17—27) are shown in blue. Residues in chain A in each protein engaged in protein-protein interactions with Aβ fragments are magenta-colored and have side chains displayed.

Table 9.B.1 Fuzzy oil drop parameters for 4MVI (with Aβ(16−28) peptide) and 4MVL (with Aβ(17−27) peptide. Asterisks mark the absence of Val18, causing a discordance. Values given in bold distinguish the status of discordance in respect to idealized hydrophobicity distribution.

		RD		Correlation coefficient		
PDB ID	**Fragment**	**T-O-R**	**T-O-H**	**HvT**	**TvO**	**HvO**
4MVI	Complex A + B	0.337	0.291	0.440	0.700	0.765
	Chain A	0.300	0.256	0.477	0.762	0.761
	Chain B	0.419	0.385	0.239	0.453	0.886
4MVI	Aβ(16−28)	0.372	0.256	0.617	0.667	0.873
Chain B	16-22	0.275	0.275	0.660	0.603	0.883
	22−28	0.227	0.227	0.869	0.886	0.933
4MVL	Complex A + E	0.319	0.290	0.449	0.709	0.747
	Chain E	0.482	0.400	−0.160	0.333	0.714
	Chain A	0.277	0.254	0.487	0.777	0.757
4MVL	Aβ (17−27)	0.446	0.400	0.173	0.513	0.705
Chain E	**17−22**	**0.595**	**0.405**	**−0.013**	**0.104**	**0.615**
	22−28	0.236	0.270	0.630	0.893	0.859
	22−28*	0.306	0.135	0.195	0.837	0.612

(lipocain + peptide), for the peptide analyzed as part of the complex, and for the standalone peptide.

As listed in Table 9.B.1, the complex as a whole exhibits low RD (Fig. 9.B.2). The Aβ chain, analyzed as a standalone unit (with a custom Gaussian capsule), is also accordant with the theoretical distribution (Fig. 9.B.3). Further analysis reveals, however, that the status of individual fragments varies. In the case of Aβ(17−27) the 17−22 fragment has amyloid-like properties: relatively high RD, low HvT and TvO, and high HvO.

Aβ(16−40) in complex with phage-display selected affibody protein Z(Aβ3)

We will now focus on the structure of Aβ(16−40) in complex with phage-display selected affibody protein Z(Aβ3) − engineered binding protein. The structure is listed in PDB as 2OTK [2].

Protein Z consists of two chains, 43 aa each, and acts as a packaging for the centrally placed Aβ(1−40) peptide. The peptide itself becomes a β-hairpin "arrested" between two mainly alpha up-down bundles (CATH code: 1.20.5.420), as defined in Ref. [6]. Both Z chains are listed as 14−56 fragments, linked with a disulfide bond (Cys28).

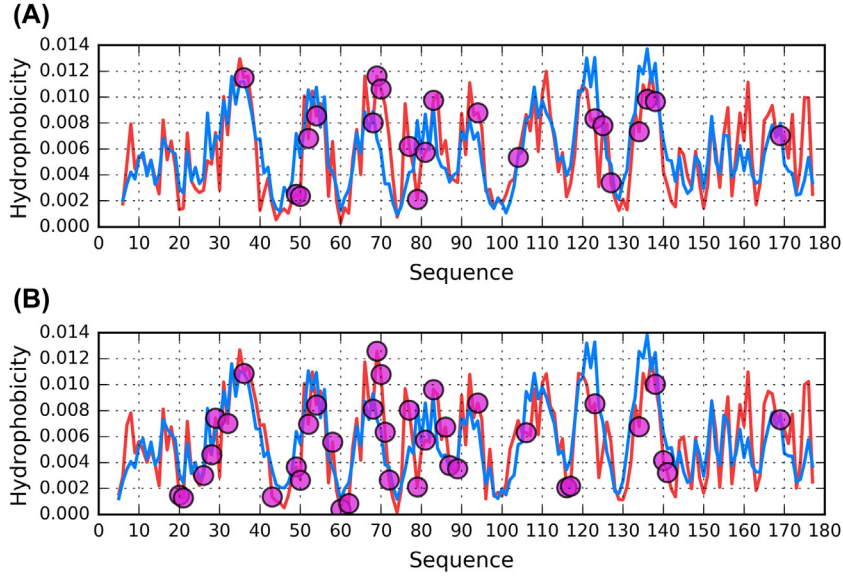

Fig. 9.B.2 Theoretical (T, blue) and observed (O, red) hydrophobicity distribution profiles for chains A of 4MVI and 4MVL analyzed as a part of complex with Aβ(1—42) peptides. (A) 4MVI. (B) 4MVL. Magenta circles denote residues engaged in protein-peptide interactions.

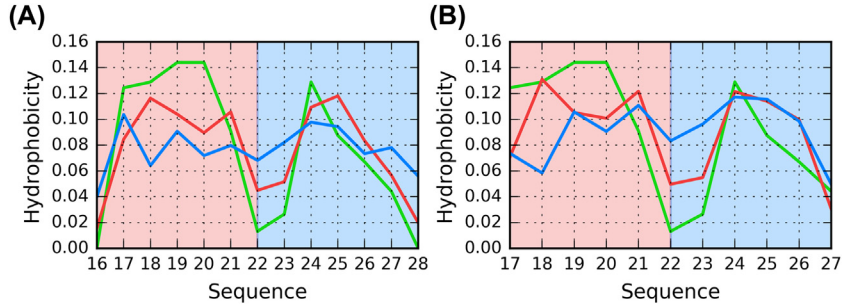

Fig. 9.B.3 Theoretical (T, blue), observed (O, red) and intrinsic (H, green) hydrophobicity distribution profiles for Aβ(1—42) peptides from 4MVI and 4MVL analyzed as individual units. (A) Aβ(16—28) — chain B (B) Aβ(17—27) — chain E. Colored background denotes fragments which correspond to the building blocks of Aβ(1—42) amyloid structures: 16/17—22 — red, 22—27/28 — blue.

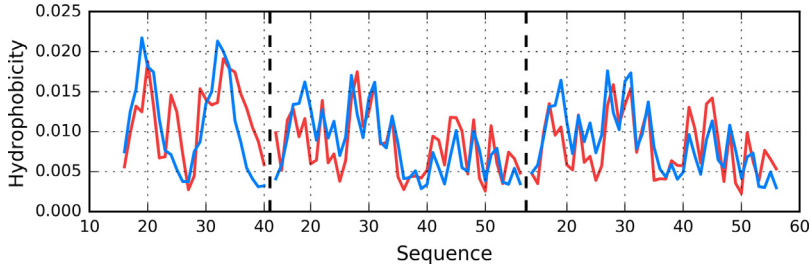

Fig. 9.B.4 Theoretical (T, blue) and observed (O, red) hydrophobicity distribution profiles for 2OTK complex. Dashed vertical lines mark boundaries between the chains (from left to right: C, E, F). Chain C represents the Aβ(16—40) peptide. Protein-protein contacts are not shown here due to the fact that nearly all residues from chain C interact with the other two chains.

Chains E and F belong to protein Z, while chain C is the Aβ(16—40) peptide.

Fig. 9.B.4 illustrates the theoretical and observed hydrophobicity distribution in the Z(Abeta3) complex. Note the similarities between protein Z chains (E and F) and the differing C chain.

Table 9.B.2 provides quantitative data — specifically, RD parameters and correlation coefficients for all presented structures.

Table 9.B.2 Fuzzy oil drop parameters for 2OTK. Chain C corresponds to Aβ(16—40). Values listed in boldface mark deviations from theoretical predictions in favor of amyloid-like conditions.

		RD		Correlation coefficient		
PDB ID	**Fragment**	**T-O-R**	**T-O-H**	**HvT**	**TvO**	**HvO**
2OTK	Complex E + F + C	0.407	0.328	0.558	0.702	0.803
	Complex E + F	0.370	0.335	0.622	0.728	0.864
	Chain E	0.391	0.340	0.603	0.880	0.709
Chain C	In complex	0.660	0.319	0.397	0.613	0.650
	16-22	0.241	0.049	0.804	0.776	0.824
	22—28	**0.578**	0.262	**−0.394**	**0.055**	**0.836**
	28—40	0.700	0.572	0.171	0.720	-0.173
	28—32	0.522	0.163	0.808	0.456	0.816
	32—40	0.675	0.583	0.140	0.764	-0.130
Chain C	Individual	0.591	0.290	0.279	0.493	0.602
	16—22	0.694	0.177	0.164	0.346	0.884
	22—28	**0.613**	0.356	**−0.305**	**−0.018**	**0.866**
	28—40	0.571	0.237	0.220	0.658	0.260

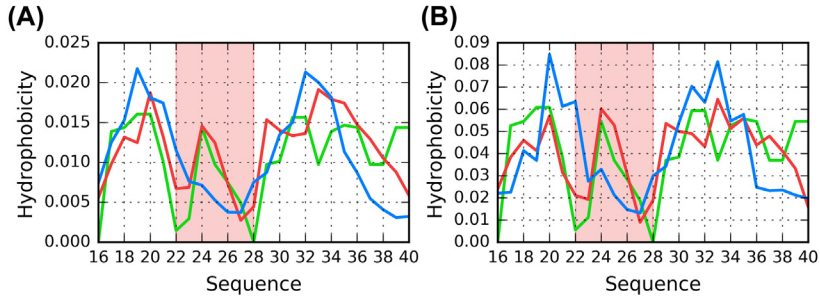

Fig. 9.B.5 Theoretical (T, blue), observed (O, red) and intrinsic (H, green) hydrophobicity distribution profiles for chain C of 2OTK corresponding to Aβ(16−40). (A) as a component of the Z complex. (B) as a standalone unit. The 22-28 fragment is highlighted as a potential amyloid seed due to its strong discordance.

Values listed in Table 9.B.2 suggest that the complex as a whole contains an ordered hydrophobic core, as evidenced by low RD and balanced correlation coefficients. The same is true for chains E and F, which "package" chain C.

Regarding chain C itself (Fig. 9.B.5), it deviates from the theoretical distribution both as a component of the protein complex and as a standalone structure. In attempting to identify the causes of this discordance we have computed RD parameters and correlation coefficients for fragments of the Aβ(16−40) chain which meet the amyloid seed criteria. These values, listed in Table 9.B.2, indicate that the fragment at 23−28 may be characterized as amyloid-like, with high RD(T-O-R), high HvO and very low HvT and TvO, even dipping into the negative territory. All these properties are consistent with an amyloid seed [7,8].

While the C chain as a whole is aligned with the structure of the Z complex, the 22−28 fragment retains its peculiar amyloid-like properties, similar to those observed in the Aβ(16−40) amyloid. Its exposed location within the complex is highlighted in Fig. 9.B.6.

Aβ(1−40) in complex with polyphenol ε-viniferin glucoside (EVG)

PDB lists two forms of Aβ(1−40) in complex with polyphenol ε-viniferin glucoside (EVG), differing with respect to the interaction site (i.e. the residues which engage the ligand): 2M9R and 2M9S [3].

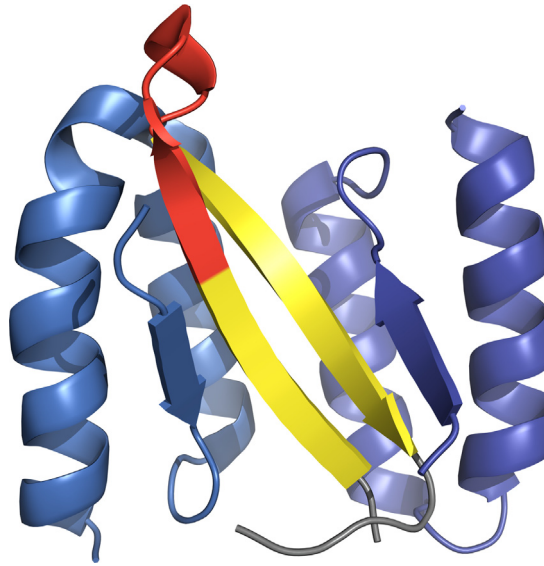

Fig. 9.B.6 3D presentation of 2OTK complex of three chains: E (blue), F (marine) and C – the Aβ(16–40) peptide (gray/yellow). Red color marks the 22–28 fragment of this chain. Protein-protein contacts are not shown here due to the fact that nearly all residues from chain C interact with the other two chains.

Table 9.B.3 provides a quantitative summary of both forms. In each case RD remains very high as a result of the random-coil conformation adopted by the chain. Interpretation of the remaining parameters is essentially out of scope of the fuzzy oil drop model, since no tertiary structure can be observed. As already suggested, the model is invoked here only to provide a common platform for comparative structural analysis.

Table 9.B.3 Fuzzy oil drop parameters for 2M9R and 2M9S. The residue numbers given in bold distinguish those of amyloid character in amyloid fibrils (Chapter 10).

		RD		Correlation coefficient		
PDB ID	**Fragment**	**T-O-R**	**T-O-H**	**HvT**	**TvO**	**HvO**
2M9R		0.852	0.857	0.050	−0.051	0.630
	16–22	0.447	0.284	0.463	0.410	0.895
	22-28	0.490	0.146	0.490	0.405	0.762
	29-40	0.968	0.913	0.130	−0.046	−0.398
2M9S		0.789	0.769	−0.022	−0.071	−0.632
	16-22	0.455	0.544	0.545	0.537	0.952
	22-28	0.366	0.218	0.521	0.717	0.835
	29-40	0.966	0.884	0.080	−0.406	−0.391

It is difficult to directly interpret the values listed in Table 9.B.3 due to the lack of a tertiary conformation; nevertheless, we may conclude that this protein does not appear to contain any hydrophobic core, and that it also does not produce an amyloid-like structure.

While the theoretical distribution of hydrophobicity is expected to contain one global maximum, multiple local maxima are observed instead (Fig. 9.B.7). This replacement of a large maximum with several smaller ones is a characteristic property of the Aβ(1—40) polypeptide, and is caused by the Lys residue at position 22, where high hydrophobicity is expected. A local maximum exists between residues 22 and 28. Fragments listed in boldface in Table 9.B.3 are highly discordant in amyloid conformations of Aβ(1—40) — however, they do not reveal strong discordance in either 2M9R or 2M9S.

Ligands play a crucial role in the analyzed polypeptides. The EVG molecule is strongly hydrophobic, and may act as a "substitute" hydrophobic core for the polypeptide chain. Such quasi-cores, contributed by ligands (rather than by the aqueous environment), may have a profound impact on the conformations of polypeptide chains, as evidenced by RD values for both ligand-binding and non-ligand-binding residues. As a result of the presence of EVG, the molecule becomes soluble. This suggests a possible design strategy for anti-fibril drugs.

The presence of relatively high hydrophobicity in the unstructured (loose) C-terminal fragment is intriguing.

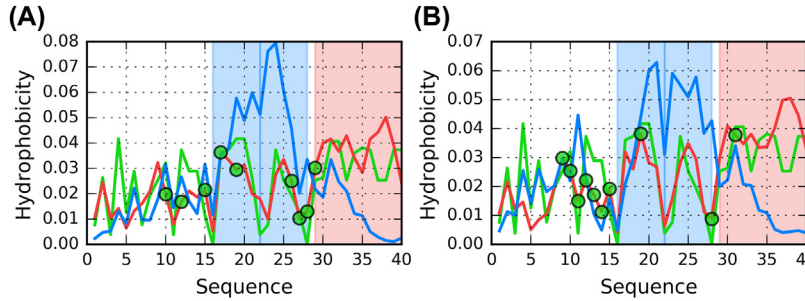

Fig. 9.B.7 Theoretical (T, blue), observed (O, red) and intrinsic (H, green) hydrophobicity distribution profiles for Aβ(1—40) complexes 2M9R and 2M9S. (A) 2M9R. (B) 2M9S. Blue background marks fragments 16-22 and 22-28 which are identified as amyloid seed in amyloid fibrils generated by Aβ(1-42) amyloid (Chapter 10A). Green circles denote resodies engaged in protein-ligand interaction.

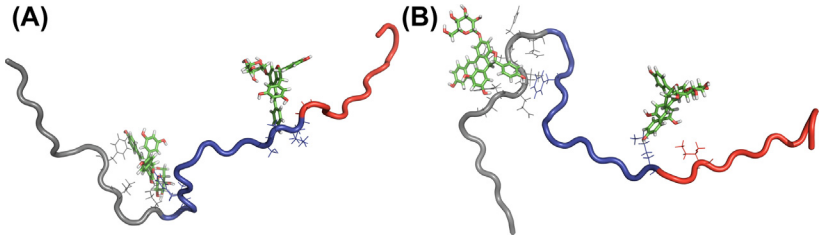

Fig. 9.B.8 3D presentation of 2M9R and 2M9S Aβ(1−40) complexes with EVG ligand. (A) 2M9R. (B) 2M9S. Fragments 16-22 and 22-28 which are treated as amyloid seeds (Chapter 10A) are given in red Residues engaged in ligand complexation are given in form of side-chains displayed.

The role of polyphenol ε-viniferin glucoside (EVG) as a permanent chaperone involves interaction with the central part of the chain (Fig. 9.B.8), producing a conformation which prevents the protein from aggregating into long amyloid-like fibrils.

In summary, it should be underscored that the presence of ligand is essential in preventing certain structural forms of Aβ(1−40) from amyloid transformation. The Lys residue at position 22 introduces structural disorder, which makes it difficult to generate a centralized hydrophobic core. This explains the presence of two local hydrophobicity maxima instead of a single global maximum. Engagement of fragments located on either site of the Lys residue prevents linear propagation, which would otherwise be possible. Thus, the ligand exerts a profound influence on the conformation of the presented chains. In line with the hypothesis formulated in Ref. [3], EVG appears to play the role of a protector against amyloid formation.

The presented analysis may be criticized as inadequate given that the sample polypeptides are incapable of producing globular structures (which is a prerequisite of applicability of the fuzzy oil drop model). Applicability of fuzzy oil drop model to molecules which do not generate the tertiary structure is not reasonable. This analysis was performed anyway to make the analysis of polypeptides discussed in this chapter complete. This example can be taken as the example to complete wide spectrum of different structural forms treated as targets for fuzzy oil drop model. However, we have decided to include them in order to broaden our study of the various forms adopted by the Aβ(1−40) polypeptide. In particular, comparing amyloid-like and non-amyloid-like structures which share identical sequences is of great theoretical interest. The applied model enables assessment of arbitrary

molecules with regard to their hydrophobicity distribution − a factor strongly implicated in amyloidogenesis [7,8].

Aβ(1−21) in complex with the JEF ligand

The PDB file with ID 5HOX lists the Aβ(1−21) chain in a hexamer (six β-hairpins) complex with the JEF ligand − *O-(O-(2-Aminopropyl)-O'-(2-Methoxyethyl)polypropylene glycol 500) [Jeffamine]* ($C_{30}H_{63}NO_{10}$) [4]. All hairpins have the same sequence and share a similar structure. The ligand is centrally located, which suggests its role in coordinating the complex.

Table 9.B.4, (Figs. 9.B.9 and 9.B.10) characterizes the whole peptide as well as selected structural folds comprising the β-hairpin. The fragment at 2−10 exhibits strong amyloid-like properties (Fig. 9.B.9). To enable

Table 9.B.4 Fuzzy oil drop parameters for chain A of 2OTK. Values listed in boldface deviate from theoretical predictions in favor of amyloid-like conditions. The underlined fragment is regarded as weakly amyloid-like.

		RD		Correlation coefficient		
PDB ID	**Fragment**	**T-O-R**	**T-O-H**	**HvT**	**TvO**	**HvO**
5HOX	1-21	0.554	0.216	0.204	0.603	0.767
	2-10	**0.803**	**0.545**	**−0.455**	**−0.252**	**0.762**
	13-21	0.484	0.116	0.221	0.796	0.657
	(2−10) + (13−21)	**0.677**	**0.282**	**−0.092**	**0.390**	**0.697**
	16-21	0.655	0.580	−0.167	0.896	0.131

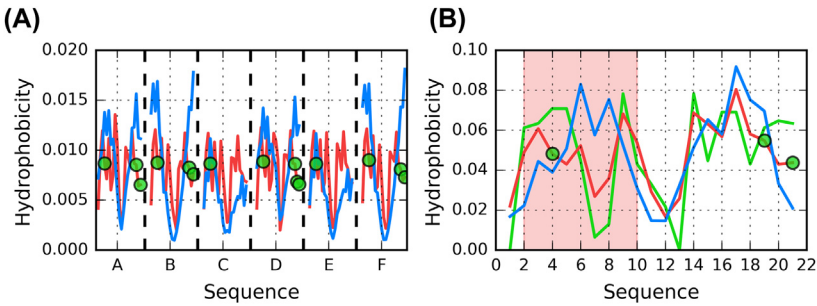

Fig. 9.B.9 Theoretical (T, blue), observed (O, red) and intrinsic (H, green) hydrophobicity distribution profiles for 5HOX. (A) for every chain as a part of the complex. (B) for chain A as individual unit. Red background distinguishes fragment at 2−10 with strong amyloid-like properties. Green circles denote residues engaged in protein-ligand interactions.

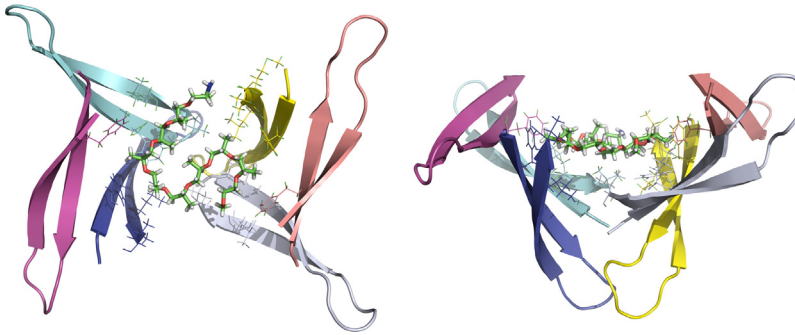

Fig. 9.B.10 3D presentation of 5HOX hexamer from two angles, revealing the crucial role of the JEF ligand in coordinating the β-hairpin complex. Each chain is presented in different color. Residues engaged in protein-ligand interactions have side chains displayed.

comparisons with other peptides and amyloids, we also distinguish the fragment at 16−21, which may be described as weakly amyloid-like.

The deviation identified at 2−10 consists of two local maxima where only a single maximum is predicted by the theoretical model. The existing local maxima are also broader than the expected single maximum. For example, at position 9 the theoretical distribution expects a gradual decline in hydrophobicity; however a local peak is observed instead − effectively "in opposition" to T. Such conditions are common in amyloids.

Aβ(18−41) fragment inserted as the antigen receptor variable domain in shark immunoglobulin

In this example, the Aβ(18−41) fragment constitutes the antigen receptor variable domain in shark immunoglobulin [5]. It is listed in PDB as 3MOQ.

From among all fragments discussed in this chapter this particular fragment has the fewest degrees of freedom. It is inserted into the V domain of immunoglobulin G, which fixes its N- and C-terminal sections − even though its overall length (33 aa) admits flexible rearrangements, since the fragment is classified as a hypervariable loop, which must align itself to the target antigen in order to perform its biological function.

As expected by the authors, a non-amyloid structural form of Aβ(18−41) has been obtained and found to resist aggregation. While fixed on both ends, it nevertheless retains some structural flexibility, enabling us to study its conformational preferences (Table 9.B.5).

Table 9.B.5 Fuzzy oil drop parameters for 5HOX. Underlined values indicate a weakly amyloid-like fragment.

		RD		Correlation coefficient		
PDB ID	**Fragment**	**T-O-R**	**T-O-H**	**HvT**	**TvO**	**HvO**
3MOQ	88—111 Aβ(18—41)	0.682	0.691	0.093	0.302	0.670
	18—22	0.207	0.496	0.680	0.830	0.818
	22—28	0.511	0.299	−0.105	0.340	0.781

The characteristic presence of Lys98 seen in Fig. 9.B.11 creates a local minimum where a participation in maximum is expected instead (92—106). However in this structure, the lysine residue is only partially exposed on the surface (Fig. 9.B.12) remaining close to the center, where hydrophobicity should otherwise remain high. This amyloid-like deviation, while not clearly revealed in the whole-domain plot, becomes notable when the Aβ(18—41) fragment is studied on its own.

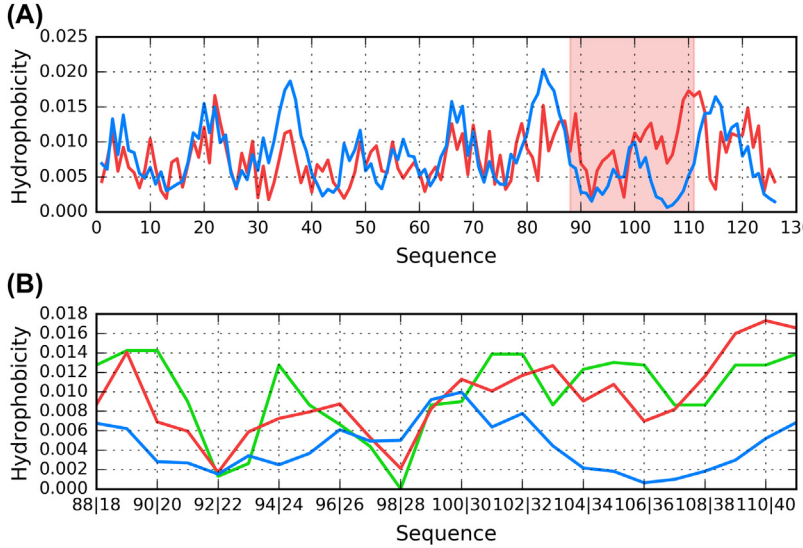

Fig. 9.B.11 Theoretical (T, blue), observed (O, red) and intrinsic (H, green) hydrophobicity distribution profiles for 3MOQ. (A) complete chain with Aβ(18—41) fragment highlighted in red. (B) Aβ(18—41) fragment (residues 88—111). Dual labels on the horizontal axis of B list PDB residue numbers (first value) and positions relative to Aβ(18-41) (second value).

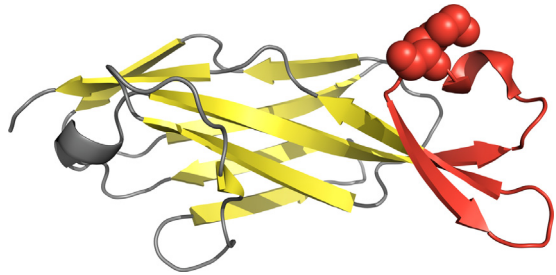

Fig. 9.B.12 3D presentation of 3MOQ, with the Aβ(18—41) fragment (residues 88—111) marked in red. Position of Lys98 in this fragment is highlighted with space-filling display style.

Discussion and conclusions

Fig. 9.B.13 provides a comparative overview of the similarities and differences between proteins discussed in this chapter.

Fig. 9.B.13 underscores the key role of the ligand or peptide with which the protein interacts. β-fragments found in 2OTK and 5HOX are almost fully engaged in interaction with the encapsulating protein — their permanent chaperone. 4MVI, 4MVL, 2M9R and 2M9S are all characterized as

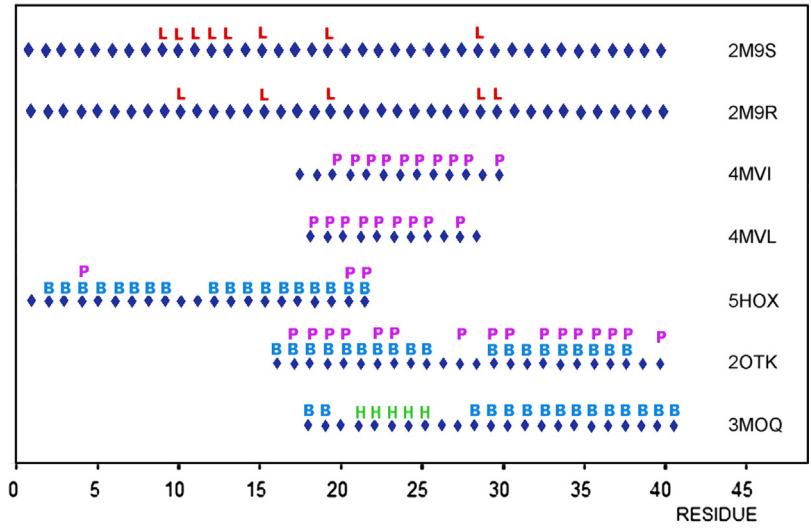

Fig. 9.B.13 Comparison of Aβ(1—42) fragments present in each analyzed structure. Specific ranges are indicated by the lower horizontal bars for each table entry. L — ligand binding, P — protein-peptide interactions, B — sheet, H — helix.

random coils. In the two former cases they also remain in full contact with external complexation partners. With regard to 2M9R and 2M9S, the presence of ligands appears to have a decisive influence on structural stability, likely due to steric hindrance (as a relatively large molecule the ligand effectively prevents complexation). In addition, by engaging residues which are quite far apart in the chain, the ligand forces it to adopt a random coil (and therefore non-amyloid-like) conformation.

The β-hairpin found in 5HOX (at 2−10) exhibits amyloid-like properties, while the fragment at 16−21 is characterized by high RD and high HvT, but also by high TvO. Consequently, it may be regarded as "weakly amyloid-like". Other fragments whose FOD status is similar to that found in amyloids include 22−28 in 2OTK and 17−22 in both 4MVL and 4MVI. As noted above, 2M9R and 2M9S do not appear to contain any amyloid-like fragments.

A common property of all presented forms of the Aβ(1−42) peptide is the need for an external factor which guides the folding process. The complexes described in this chapter were identified while seeking structural factors capable of arresting the growth of amyloids. In all cases, this is achieved by interaction with an external ligand or protein, producing a structure which does not permit unrestricted aggregation resulting in amyloid formation.

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