Dynamics of Amyloid β Fibrils Revealed by Solid-state NMR

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Holger A. Scheidt, Isabel Morgado, Sven Rothemund, and Daniel Huster

From the Institute of Medical Physics and Biophysics, University of Leipzig, D-04107 Leipzig, Germany, the Institute of Biochemistry/Biotechnology, Martin Luther University Halle-Wittenberg, D-06120 Halle, Germany, and the Interdisciplinary Center for Clinical Research, University of Leipzig, D-04103 Leipzig, Germany

Background: Alzheimer disease is the most important neurodegenerative disorder; treatment approaches require atomistic knowledge of fibrillar structure and dynamics.

Results: We have site-specifically studied the molecular dynamics of amyloid β (Aβ) fibrils by solid-state NMR.

Conclusion: The β-sheet motifs of Aβ are essentially rigid, and the termini exhibit more flexibility.

Significance: Dynamics studies of Aβ fibrils suggest a structural role of the N terminus of the peptide.

We have investigated the site-specific backbone dynamics of mature amyloid β (Aβ) fibrils using solid-state NMR spectroscopy. Overall, the known β-sheet segments and the turn linking these two β-strands exhibit high order parameters between 0.8 and 0.95, suggesting low conformational flexibility. The first approximately eight N-terminal and the last C-terminal residues exhibit lower order parameters between ~0.4 and 0.8. Interestingly, the order parameters increase again for the first two residues, Asp1 and Ala2, suggesting that the N terminus could carry some structural importance.

Alzheimer disease represents the most widespread neurodegenerative disease affecting particularly the countries with high life expectancy. The existence of extracellular deposits of amyloid fibrils formed from amyloid β (Aβ) peptides represents a hallmark of the disease. These deposits constitute the end product of a complicated aggregation pathway that initiates with Aβ monomers, which are the result of the action of several enzymes on the amyloid precursor protein. The folding of Aβ monomers into mature Aβ fibrils occurs via transient oligomeric and protofibrillar states, which are considered to be the toxic intermediates in the disease.

Detailed structural data on mature Aβ fibrils have been provided by solid-state (1–5) and solution (6, 7) NMR spectroscopy, as well as by cryo-electron microscopy (8, 9). It is well established that Aβ fibrils exhibit a significant amount of structural polymorphism (10–13). Part of this polymorphism is due to preparation conditions, but surprisingly, most structural studies seem to agree on a general U-shaped β-strand-turn-β-strand motif of the Aβ peptides in fibrils, with some variation in the register of the opposing β-strand zippers (5, 14).

In addition, NMR structural data are now available for various Aβ aggregation intermediates, including protofibrils (15) and oligomers (16–18). Interestingly, the molecular dynamics of Aβ fibrils, which is an essential part of the structural biology of amyloid structures, has not been comprehensively studied. In fact, only a very few reports on fibrillar dynamics in general exist so far (15, 19, 20). These studies showed that the investigation of the fibril dynamics can significantly support the structural analysis and further characterize the respective structural elements. The combination of structural and dynamical analysis leads to a much more complete picture of the structural biology of the fibrils and therefore improves the understanding of the fibrillation process and the mode of action of the investigated structures. Here, we have studied the molecular dynamics of mature Aβ(1–40) fibrils in a site-specific manner using solid-state NMR spectroscopy.

**EXPERIMENTAL PROCEDURES**

**Sample Preparation**—For this investigation, eight Aβ(1–40) peptides with uniformly 13C/15N-labeled amino acids in different positions were synthesized using standard N-(9-fluorenylethoxycarbonyl) protocols. The individual Aβ(1–40) peptides with sequence DAEFRHDSGYEVHHQKLVFFAEDV

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liquid nitrogen and thawing it at 37 °C. TEM samples were prepared by applying 5-ml droplets from the sample after 1:10 dilution with pure water onto a carbon film (floating carbon method), counterstained with 2% (w/v) uranyl acetate, and analyzed with a Zeiss 900 electron microscope (80 kV).

$^{13}$C Magic Angle Spinning (MAS) NMR Measurements — The $^{13}$C cross-polarized MAS NMR spectra were measured on a Bruker AVANCE 750 spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) operating at a resonance frequency of 749.7 MHz for $^1$H and 188.5 MHz for $^{13}$C. A 4-mm double-resonance MAS probe was used. The cross-polarized contact time was 700 μs; typical lengths of the 90° pulses were 5 μs for $^{13}$C and 4 μs for $^1$H. For heteronuclear two-pulse phase modulation decoupling, a $^1$H radiofrequency field of 65 kHz was applied. $^{13}$C chemical shifts were referenced externally relative to TMS. Two-dimensional $^{13}$C-$^{13}$C proton-driven spin exchange spectra with a mixing time of 50 ms were acquired for peak assignment (21).

Constant time dipolar coupling and chemical shift (DIPSHIFT) experiments using frequency-switched Lee-Goldberg homonuclear decoupling (80-kHz decoupling field) were carried out to measure the $^{13}$C-$^1$H dipolar couplings (22). DIPSHIFT experiments were conducted as two-dimensional measurements, where each increment in the indirect dimension refers to one-time increment to sample the dipolar dephasing curve of the respective backbone signal. Spectra were only Fourier-transformed in the direct dimension, allowing us to directly read off the intensities of the dipolar dephasing curve in the indirect dimension for each resolved backbone signal. Thus, a single two-dimensional DIPSHIFT experiment provides the complete dipolar dephasing curve for each resolved carbon (23). After simulating the dipolar dephasing curve over one rotor period, the order parameter was derived by dividing the determined coupling by the known rigid limit (24, 25). All experiments were carried out at a temperature of 303 K and a MAS frequency of 7 kHz.

RESULTS

Aβ(1–40) fibrils were grown in 50 mM sodium borate buffer at pH 9. To assess the morphological homogeneity of the samples used in this study, Fig. 1 shows typical TEM pictures of four different preparations. TEM pictures of all eight peptide preparations are shown in supplemental Fig. S1.

This choice of buffer system provided the most homogeneous Aβ preparations as can be assessed from the TEM pictures. We also compared the NMR spectra of Aβ(1–40) fibrils grown in sodium borate buffer at pH 9 with fibrils grown in sodium phosphate buffer at pH 7.4 (data not shown). The NMR spectra from both fibril preparations showed signals with identical chemical shifts; however, the fibrils prepared in borate buffer provided slightly narrower lines in the NMR spectra. Therefore, we continued our investigations with this system.

To study the molecular dynamics of Aβ fibrils, we carried out solid-state NMR experiments. The DIPSHIFT pulse sequence (22) allowed us to measure the molecular order parameters of mature Aβ(1–40) fibrils prepared from the eight differently $^{13}$C/$^{15}$N-labeled peptides in a site-specific manner. From this measurement of the backbone $^{13}$C-$^1$H dipolar couplings, we determined the backbone order parameters to characterize the amplitude of motion for the Cα–Hα bond vectors. A fully rigid C–H bond would exhibit the maximal dipolar coupling strength of 22.8 kHz, corresponding to an order parameter of 1, whereas a value of 0 for the order parameter corresponds to fully isotropic motion expressed by a vanishing dipolar coupling. Molecular motions with a given amplitude lead to partial averaging of the dipolar coupling and can be characterized by a specific order parameter. The $^{13}$C-$^1$H order parameters sample all motions with correlation times shorter than $\sim 10$ μs. A plot of the backbone order parameter in mature Aβ fibrils at a hydration level of 50 weight % for the Cα atoms calculated from the measured couplings is shown in Fig. 2. Overall, the order parameters for the mature Aβ fibrils are rather high and never drop below 0.4. Typical dipolar dephasing curves of the MAS signals used for the determination of these order parameters of the Aβ preparations are given in supplemental Fig. S2. For Ile$^{32}$ and Val$^{60}$, two slightly different order parameters were determined from the NMR signals that exhibited two sets of isotropic chemical shifts. This corresponds to some structural heterogeneity within the fibrils that has already been observed in previous studies (2, 3). We also carried out DIPSHIFT measurements on fibrils prepared at a hydration level of 75 weight % (data not shown). Within experimental error, no differences in the order parameters at these two hydration levels were found.

To correlate these order parameters with secondary structure motifs in Aβ fibrils, we carried out $^{15}$C-$^{13}$C correlation experiments and analyzed the isotropic chemical shifts of the $^{13}$C MAS NMR spectra of the individual Aβ preparations. Typical $^{13}$C MAS NMR spectra of our preparations are shown in supplemental Fig. S3. A plot of the secondary chemical shifts (i.e. the chemical shift deviation of a given residue from the random coil values) presented in Fig. 3 shows random coil-like chemical shifts at the peptide N terminus (residues 1–4 and 6–9). In addition, we found two β-sheet regions, comprising residues 11–22 and 30–38, which are connected by a segment with random coil-like chemical shifts, involving residues 23–29. Our isotropic chemical shift data (supplemental Table S1) agree well
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FIGURE 2. Plot of $^{13}$C-$^1$H order parameters for mature Aβ(1–40) fibrils at hydration level of 50 weight % as determined from quantitative measurements of $^{13}$C-$^1$H dipolar couplings by DIPSHIFT experiment. Regions with a known β-sheet structure are highlighted. The error bars represent the uncertainty of the fitting procedure of the MAS time domain signals.

FIGURE 3. Secondary $^{13}$C MAS NMR isotropic chemical shift values for Ca (●) and Cβ (○) for mature Aβ(1–40) fibrils at hydration level of 50 weight %. Data are given as the difference between a measured chemical shift for a specific amino acid and random coil chemical shifts taken from literature. Regions that are in agreement with β-sheet secondary structure are highlighted.

FIGURE 4. Plot of $^{13}$C MAS NMR line widths (full-widths at half-maximum) for Ca (●) and Cβ (○) for mature Aβ(1–40) fibrils at hydration level of 50 weight %. Regions that are in agreement with β-sheet secondary structure are highlighted.

with existing literature values obtained with other samples of mature Aβ(1–40) fibrils (1–5). This suggests a very similar secondary structure of the fibrils grown in borate buffer compared with the known models. We further note that the region connecting the two β-strands exhibits secondary chemical shifts that are highly variable and show multiple sets of chemical shifts at several positions (supplemental Table S1), which was also observed in previously reported Aβ(1–40) fibril preparations (2, 3). Collectively, these data indicate that the intervening loop connecting the two β-sheets is affected by significant structural polymorphism. As previous chemical shift measurements were carried out with samples that were obtained under significantly different fibrillation conditions and procedures, the presently observed similarities confirm that Aβ peptides adopt a rather well conserved peptide fold even when fibrillated under somewhat different physicochemical conditions.

Comparison of the order parameters determined in this study with the identified secondary structural elements shows that the two β-sheet regions, along with the intervening loop, exhibit relatively high order parameters of 0.8–0.95. Such values are indicative of a very rigid peptide backbone structure. Such high order parameters would correspond to segmental motions with amplitudes of ~15–30°. This is also consistent with previous evidence that a salt bridge between Asp23 and Lys26 (14, 26) stabilizes this short connection and prevents larger backbone motions. The high order parameter values observed for the two central β-sheet regions also correspond well with literature data on the order of PABPN1 fibrils (19) and fibrils of the human prion protein (20).

Slightly lower order parameters (≤0.8) were obtained at the peptide N and C termini (residues 1–4, 7, and 40). This finding indicates that the terminal ends of the mature Aβ fibrils are less well structured than the more central regions.

A particularly striking result of our data set is the fact that the first two residues in the Aβ sequence (Asp1 and Ala2) exhibit significantly higher order parameters than the subsequent amino acid (Glu3). This appears to be a very unique feature of the Aβ fibrils that is very unusual and generally not known for soluble proteins.

We have also determined the line width of the NMR signals in the respective spectra of Aβ(1–40) fibrils (Fig. 4). Line widths represent a simple measure of the molecular dynamics and have also been analyzed for Aβ fibrils previously (21). The line widths for the labeled residues typically vary between ~1 and 3 ppm, with only Ser8 showing a value of ~4.5 ppm. There was no clear trend for an increase in the line width toward the N terminus.

DISCUSSION

We have studied the molecular dynamics of mature Aβ(1–40) fibrils by solid-state NMR spectroscopy. $^{13}$C MAS NMR chemical shifts detected for the Aβ fibrils studied here agreed well with what has been observed in the literature (1–5). In addition, we have presented a site-specific study of the molecular dynamics of the Ca backbone carbons. The dynamics data are presented as order parameters that provide information about the motional amplitude of the Ca–H bond vector in the protein backbone. A schematic projection of the order parameter values onto the known topology of Aβ fibrils is given in Fig. 5. Collectively, these data indicate the existence of signifi-
cant structural stability at the peptide N terminus, which specifically affects the first two residues.

At first sight, the motional analysis of the mature Aβ fibrils reveals no significant surprises. The two central β-strand elements exhibit high order parameters; molecular order is somewhat decreased in the connecting loop region and the N and C termini, respectively.

However, two results of the motional analysis are particularly noteworthy: both concern the N terminus of the mature Aβ fibrils. First, the measured order parameters for the N terminus are still significantly higher than those associated with a purely thermally fluctuating random coil (which is typically ~0.1–0.3 even under solid-state conditions) (19). Moreover, such low order parameters would be expected to abolish or to strongly attenuate the cross-polarization signal of these protein parts (27), which was not observed here. Perhaps the tendency of Aβ peptides to form an additional β-strand for amino acids 4–7, which was also observed in some structural studies by solid-state (5) and solution (7) NMR or molecular dynamics simulation (28), can explain the absence of high molecular dynamics in this region. Second, the fact that the order parameters of the first two residues (Asp and Ala) are actually higher than for Glu suggests that the N terminus represents a somewhat structurally confined segment that may also be stabilized in the course of peptide aggregation.

The molecular dynamics of mature Aβ fibrils has not been systematically studied so far. Therefore, a comparison of our results with the literature can only be done on the basis of a 13C MAS NMR line width measurement carried out previously (1). This analysis reported large line widths of 3–5 ppm for the first ~10 N-terminal residues, whereas the remainder of the sequence showed line widths of ~2 ppm. This was interpreted as a structurally disordered N terminus. Although the line widths for our preparations of Aβ fibrils were rather homogeneous between 1 and 3 ppm over the entire peptide sequence (Fig. 4), we measured consistently lower order parameters for the N-terminal residues compared with the β-sheet and turn regions. Although the NMR line widths reflect both static structural heterogeneity and the influence of molecular dynamics, order parameters depend only on the fast protein dynamics. This supports the view that the N terminus of the Aβ fibrils is indeed more mobile than the rest of the protein; however, it does not represent a freely fluctuating polypeptide chain, which would have expressed lower order parameters.

A recent molecular dynamics simulation showed that the conformational flexibility in the loop region of the mature Aβ fibrils is not significantly increased in comparison with the two opposing β-sheets (29), which is also reflected in our experimental work. In the simulation, the conformational dynamics of the residues in the Aβ sequence increased toward the N terminus, starting at about Val12. Unfortunately, the first eight residues in the Aβ sequence were omitted in the simulation, so no comparison with the interesting dynamical behavior of these amino acids in the sequence observed in our experiments is possible.

Finally, we compared our data with a recently published study on the structure and dynamics of Aβ protofibrils (15). The order parameter profiles for the two Aβ species show a high degree of agreement for most of the amino acids (supplemental Fig. S4), and deviations are mostly within the experimental error. Only Val12 and Lys16 show slightly higher order parameters in mature fibrils compared with protofibrils. This is probably caused by the reduced length of the first β-sheet in protofibrils (15), which begins at residue 16 in protofibrils but already at residue 10 in mature Aβ fibrils (1, 5). At the N terminus, the order parameters of the first two residues in protofibrils are again larger than for residue 3, underlining the putative importance of the N terminus in peptide aggregation and fibril formation. In fact, Asp exhibits yet a higher order parameter of 0.75 in Aβ protofibrils compared with 0.65 in mature Aβ fibrils. Also Phe has a higher value of 0.79 in protofibrils compared with our data on mature Aβ fibrils (0.61). Altogether, these results may suggest that the N terminus of the Aβ peptides could play a role in the maturation of Aβ fibrils. This is particularly interesting as, structurally, protofibrils show a stronger resemblance to oligomers than to mature Aβ fibrils (15). Dynamically, however, protofibrils are actually very similar to the mature Aβ fibrils, with the most pronounced differences in the N-terminal region. A next important step would certainly
be a comprehensive dynamical characterization of \( \alpha \beta \) oligomers.

In summary, our data provide a comprehensive description of the fast molecular dynamics of mature \( \alpha \beta \) fibrils, showing that the two \( \beta \)-sheets and the turn region linking these two structural elements are essentially rigid and well ordered. The termini undergo somewhat more dynamic reorientation; however, the first two N-terminal amino acids are again slightly more ordered, suggesting that this protein part could actually play a role in the structural biology of \( \alpha \beta \) fibrils. Although it is known that the N terminus of \( \alpha \beta \) peptides does not play an important role in fibril growth (1, 30), the current data suggest that this protein part is less mobile than typically assumed and might be worth some additional attention.

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