Oxidation of Methionine 35 Attenuates Formation of Amyloid β-Peptide 1–40 Oligomers*

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Amyloid plaques formed by aggregation of the amyloid β-peptide (Aβ) are an intrinsic component of Alzheimer disease pathogenesis. It has been suggested that oxidation of methionine 35 in Aβ has implications for Alzheimer disease, and it has been shown that oxidation of Met-35 significantly inhibits aggregation in vitro. In this study, the aggregational properties of Aβ-(1–40) before and after Met-35 oxidation were investigated using electrospray ionization Fourier transform ion cyclotron resonance mass spectrometry. The results show that Aβ-(1–40)Met-35(O) trimer and tetramer formation is significantly attenuated as compared with Aβ-(1–40). This suggests that oxidation of Met-35 inhibits a conformational switch in Aβ-(1–40) necessary for trimer but not dimer formation. Random incorporation of Aβ-(1–40) and Aβ-(1–40)Met-35(O) in homo- and heterooligomers could also be observed. This is the first report of an early rate-limiting step in Aβ-(1–40) aggregation. Slowing of the fibrillation process at this early step is likely to support prolonged solubility and clearance of Aβ from brain and may reduce disease progression.

Amyloid β-peptide (Aβ)3 is a 39–43 amino acid long peptide derived from a larger transmembrane protein, the amyloid precursor protein. Aβ is the central component of neuritic plaques in Alzheimer disease (AD) brain. A large number of studies have focused on the structure, aggregational properties and fibril formation (1–5), and neurotoxicity (6, 7) of Aβ peptides and their roles in AD.

Chemical analysis of human neuritic plaques reveals a complex mixture of chemically altered Aβ deposited along with glycoproteins, glycolipids, and other ancillary components (3). Oxidized methionine, in position 35 (Met-35) of Aβ, methionine sulfoxide (Met-35(O)), has been detected in samples extracted from post-mortem AD plaques (8). These findings have yet to be extended, eradicating the possibility of a post-mortem delay or a preparatively induced oxidation artifact before in vitro extrapolation may be made. Few studies have explored the consequences of Met-35 oxidation on peptide chemical characteristics or biological actions. There are, however, some intriguing findings and some contradicting reports. Substituting synthetic Aβ1–42 with methionine sulfoxide Met-35(O) results in enhanced Aβ1–42-mediated cellular toxicity (9, 10). Whether these actions are a consequence of attenuated (11) or accelerated (10) fibril formation remains to be determined. Aβ-(1–40)Met-35(O) is dramatically less prone to aggregation and fibril formation as compared with Aβ-(1–40), shown in circular dichroism studies (12). This is also reflected by the inhibition of conformational switching of Aβ-(1–40)Met-35(O) from random coil to β-sheet, observed using millimolar peptide concentrations and NMR (12). The inhibited aggregation can, however, be overcome by increasing the concentration of Aβ-(1–40)Met-35(O).5 Using size exclusion chromatography and oxidation of Aβ-(1–40) with H2O2, we have verified the attenuated fibril formation associated with Aβ-(1–40)Met-35(O). However, the structural and conformational changes underlying this phenomenon have not yet been identified. Peptide fibril formation is a complex multistep reaction involving the transitional formation of numerous oligomeric (13) and protofibrillar (14, 15) Aβ species. Clarification of what steps in the oligomerization cascade underlie the affected aggregation rate of Aβ-(1–40)Met-35(O) would not only increase our understanding of the fibrillation reaction but also our understanding of the forces determining peptide structure and folding. This could in turn be important for understanding the potential toxicities of different Aβ species.

This study was aimed at investigating the consequences of Met-35 oxidation on the formation of small Aβ peptide oligomers and also at attempting to find oxidation-mediated rate-limiting steps in the fibrilization cascade of the Met-35(O)-modified Aβ-(1–40) peptide using a Fourier transform ion cyclotron resonance (FTICR) mass spectrometer and a home-built electrospray device. Electrospray ionization (ESI) mass spectrometry has been used previously to detect and characterize Aβ peptides in vitro (16) as well as in vivo (17). Using gentle ESI conditions, small aggregates of Aβ-(1–40) in water can be transferred to the gas phase and detected, making it possible to monitor the aggregation of Aβ-(1–40) over time (16). The oligomer distribution detected by ESI mass spectrometry (16) is similar to that approached in the short irradiation time limit of photo-induced cross-linking experiments (18). An ad-

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vantage in using the high resolving power of a 9.4 T FTICR instrument is that homo- and heterooligomers of Aβ-(1–40) and Aβ-(1–40)Met-35(O) can be resolved. Furthermore, the sensitivity of the technique allows aggregation kinetics to be studied using nano- and micromolar concentrations of Aβ, more closely resembling the in vivo situation (19).

MATERIALS AND METHODS

Sample Preparation and Oxidation of Met-35—Aβ-(1–40) was obtained from Bachem (Bachem AG, Bubendorf, Switzerland). A 4.0 μm Aβ-(1–40) solution was prepared in deionized water/acetic acid 99:1 (v/v), pH ~3. Immediately after dissolving the peptide, an aliquot was taken out, and 30% (w/v) hydrogen peroxide in water (Merck KGaA) was added to a final concentration of 2.7% (w/v). The experiment was also reproduced using H2O and 2.7% H2O2 solutions in absence of acetic acid. Additional 2.0 μM solutions were prepared in 49.5:49.5:1 deionized water/acetonitrile/acetic acid solution (v/v/v) with and without the addition of hydrogen peroxide to a final concentration of 2.7% (w/v).

Mass Spectrometry—A homebuilt instrument controlled the direct infusion where helium gas at a pressure of 1.3 bars was used to push the sample through a 30-cm fused silica capillary with an inner diameter of 25 μm. One end of the capillary was lowered into the sample, and the other end, coated by a conductive graphite/polymer layer (20), was connected to ground, functioning as an electrospray needle. No sheath flow or nebulizing gas was used. The flow rate was 40 nL/min. The ion source was coupled to an Analytica atmosphere-vacuum interface (Analytica, Branford, CT). A potential difference of 2.0–3.0 kV was applied across a distance of 3–5 mm between the spraying needle and the inlet capillary. To confirm the formation of Aβ-(1–40)Met-35(O), the peptide was sequenced by collision-induced dissociation (21) in the capillary/skimmer region in the ESI atmosphere/vacuum interface by raising the capillary potential from ~60 to ~270 V. All mass spectra were acquired using a Bruker Daltonics (Billerica, MA) BioAPEX-94e superconducting, 9.4 T FTICR mass spectrometer (22) in broadband mode. Typically, 524,288 data points were acquired, adding a minimum of 128 spectra (~3 min of acquisition time).

RESULTS

Analysis of Aβ-(1–40) in H2O—Fig. 1 shows regions of superimposed mass spectra of Aβ-(1–40) and Aβ-(1–40)Met-35(O) (methionine sulfoxide) containing monomers, dimers, trimers, and tetramers of Aβ-(1–40) and Aβ-(1–40)Met-35(O).

The isotopic peaks of [M + 2H]2+ and the odd isotopic peaks of [M + 4H]4+ were resolved to the baseline (inset). The isotopic clusters were shifted 16.00 mass units per A, corresponding to one extra 16O.

The isotopic peaks of [Aβ-(1–40) + 2H]2+ and the odd isotopic peaks of [Aβ-(1–40) + 4H]4+ were resolved to the baseline as shown in the inset. The isotopic clusters were shifted 16.00 Da per Aβ-(1–40) monomer oxidized. The unoxidized Aβ-(1–40) spectrum was acquired between 41 and 95 min, and the Aβ-(1–40)Met-35(O) spectrum was acquired between 100 and 116 min. The intensities were adjusted to compensate for the different acquisition times. These long times are not necessary but improve the signal-to-background ratio. Similar spectra taken between 20 and 30 min show less than 1% Aβ-(1–40)Met-35(O) in the unoxidized Aβ-(1–40) sample and less than 1% unoxidized Aβ-(1–40) in the oxidized sample. Putative dehydrated species (~18 Da) were also observed, likely to be the result of aspartimide formation.3

Fig. 2 shows the C-terminal part of the sequence of Aβ-(1–40)Met-35(O) read from a series of quadruply charged b-ions (23) from the quadruply charged parent ion [Aβ-(1–40)Met-35(O) + 4H]4+ resulting from collision-induced dissociation in the capillary/skimmer region. The b-ions covering residues 3–40 could be identified in this spectrum, b31 and b32 being outside the m/z range. The mass difference between the most intense isotopic peak of b31 and the corresponding isotopic peak of b31 was found to be 147.0356 Da as compared with 147.0354 Da, the theoretical mass of Met(O) (C6H13NO3S).

### FIG. 1
Excerpts from superimposed mass spectra of 4.0 μM Aβ-(1–40) before and after oxidation induced by H2O2 showing monomers, dimers, trimers, and tetramers of Aβ-(1–40) and Aβ-(1–40)Met-35(O). The isotopic peaks of [M + 2H]2+ and the odd isotopic peaks of [M + 4H]4+ were resolved to the baseline (inset). The isotopic clusters were shifted 16.00 mass units per A, corresponding to one extra 16O.

### FIG. 2
The C-terminal part of the sequence of Aβ-(1–40)Met-35(O) can be read by comparing quadruply charged b-ions and the quadruply charged parent ion. A b-ion series covering residues 3–40 could be found in this spectrum, b31 and b32 being outside the m/z range of this measurement. The mass difference between the most intense isotopic peak of b31 and the corresponding isotopic peak of b31 was found to be 147.0356 Da as compared with 147.0354 Da, the theoretical mass of Met(O) (C6H13NO3S).

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3 U. Bartenstein, Bachem AG, personal communication.
Aggregation Properties of Aβ-(1–40) and Aβ-(1–40)Met(O) in H₂O—After dissolving Aβ-(1–40) in H₂O or in 2.7% H₂O₂ in H₂O, monomers and dimers of Aβ-(1–40) and Aβ-(1–40)Met-35(O) could be detected in the first acquired mass spectra. The monomer and dimer signal intensities were the same for Aβ-(1–40) and Aβ-(1–40)Met-35(O) (Fig. 3). Trimmers Aβ(1–40)₃ and tetramers Aβ(1–40)₄ could also be detected in the first spectra of Aβ-(1–40) in H₂O. However, trimers Aβ(1–40)Met-35(O)₃ and tetramers Aβ(1–40)Met-35(O)₄ were not found in the first spectra of Aβ-(1–40) in 3% H₂O₂ or after 27–32 min (Fig. 3). After >100 min of incubation, the Aβ-(1–40) and Aβ-(1–40)Met-35(O) trimer and tetramer signals were also similar except for the mass shift of 16 Da per Aβ-(1–40) monomer caused by oxidation of Met-35. This lag phase was associated with the formation of Aβ(1–40)Met-35(O)₃ from Aβ-(1–40)Met(O) and Aβ-(1–40)Met-35(O)₂ and has not been reported previously, although lag phases in Aβ aggregation have been observed in Aβ(1–40) and Aβ(1–42) mixtures (25, 26). Aβ-(1–40) and Aβ-(1–40)Met-35(O) could be detected at 4.0 μM, 40 nM, 4.0 nM, and 400 pM concentrations; however, trimers and tetramers could only be detected at 4.0 μM, whereas dimers could still be detected at 40 nM. As a comparison, the concentration of Aβ(1–40) is about 10 ng/ml or 2.3 nM in cerebrospinal fluid (27).

After 12 h at 21 °C, ~50% of the 4.0 μM Aβ-(1–40) had been oxidized in the absence of hydrogen peroxide (Fig. 4). The Aβ-(1–40) dimers were distributed 0.25:0.5:0.25 among Aβ-(1–40)₉, Aβ-(1–40)Aβ-(1–40)Met-35(O), and Aβ-(1–40)Met-35(O)₂ (Fig. 5), indicating random incorporation of Aβ-(1–40) and Aβ-(1–40)Met-35(O) in dimers after 12 h. Similarly, a binomial distribution 0.125:0.375:0.375:0.125 is consistent with the measured signal of Aβ-(1–40) trimers (Fig. 6), although only Aβ-(1–40)₃Aβ-(1–40)Met-35(O) and Aβ-(1–40)Aβ-(1–40)Met-35(O)₂ have significant signal-to-background ratios to be detected in this spectrum. This indicates the random incorporation of Aβ-(1–40) and Aβ(1–40)Met-35(O) also in heterotrimers formed after 12 h.

Aggregation Properties of Aβ-(1–40) in H₂O and Organic Solvent—In the absence of an oxidizing agent, different charge states of dimers, trimers, tetramers, and pentamers of Aβ-(1–40) could be detected in the mass spectra of Aβ-(1–40) in low micromolar concentrations in a typical electrospray solution of
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with the predicted structure of Aβ-(1–42) dimers where the Met-35 side chains are not located in the dimer interface (30).

From several structural predictions, Met-35 would be part of the second α-helix of the Aβ-(1–40) molecule, comprising amino acid residues 28–36 (31–33). Reportedly, Aβ-(1–40) shows predominant α-helical structure at conditions that are thought to mimic the membrane environment, including SDS and trifluoroethanol (31, 33, 34). Previously, α-helix formation of Aβ was detected in water solution (35) but not known to be a prerequisite for β-sheet formation. However, recently careful temporal CD studies by Kikitadze et al. (36) revealed that α-helical structure is formed in water solution by 18 biologically relevant forms of the Aβ peptide (including Aβ-(1–40)) as a transitory structure en route to the β-sheet structure. Interestingly, Kallberg et al. (37) have identified the so-called α/β discordance as a predictor of β-amyloid formation, including the Aβ peptide, which further strengthens the α-helix→β-sheet transition hypothesis. Aβ is, like SDS, an amphipathic molecule, and evidence was recently presented that it forms micelle-like structures (38), previously predicted to comprise a step in the fibrillization process (39). These allegedly constitute centers for fibril nucleation (38). One can therefore envision that, similarly to its dissolution by SDS, Aβ forms α-helix-competent environments on its own accord, in micelle-like aggregates, once it reaches the critical “micellar” concentration needed for this structural transition.

The amphipathic nature of Aβ stems from its relatively polar N-terminal and extremely hydrophobic C-terminal region. There is also the central hydrophobic core, composed of amino acids 17–21. These hydrophobic regions, and in particular the C-terminal residues, Ile-41 and Ala-42 of the Aβ1–42 peptide (36), are critical determinants of the aggregation rate (40, 41). The oxidation may also change the stability of the second α-helix. However, the α-helix structure of Aβ has been detected just prior to maximum β-sheet formation when preparations are rich in higher molecular weight aggregates (36). Although the effect of Met-35(O) may be substantial in these instances, it is not likely to provide an explanation of our observations given the low concentrations and short time frames used in this work and low molecular weight oligomers have been the focus of attention. Therefore, the driving force for the association of these small oligomeric structures may be more dependent on hydrophobic interactions than on secondary structural driving forces. Aβ dimer methionine sulfoxide groups pointing outwards, as suggested by molecular modeling (30) and indirectly supported by our observations, would reduce the total hydrophobic surface available for further molecular association. Interestingly, Shen and Murphy (28) have observed faster fibril growth rates in acidic acetonitrile/water solution. The secondary structure of dimers and trimers remains to be determined using direct methods such as NMR, and the discussion on α-helical contents has to be considered in this context.

In the experiments presented here, the ionization efficiencies and charge state distributions of monomer and dimers did not differ significantly between Aβ-(1–40) and Aβ-(1–40) Met-35(O) and therefore could be expected to be similar for trimers and tetramers as well, which is also supported by the fact that trimer and tetramer signal intensities are comparable after the initial lag phase. One should be cautious not to draw conclusions from the measurements of single charge states as charge state distribution can (and does, at least to a small degree) change upon oxidation of Met-35. The alteration of ionization efficiency and charge state distribution are possible sources of artifacts in electrospray ionization and could be caused by slight shifts in pH or altered potentials in the atmosphere/vacuum interface due to contamination.

**DISCUSSION**

These results suggest that oxidation of Met-35 inhibits a conformational switch of Aβ-(1–40) necessary for trimer formation but also that this conformational change does not significantly affect the formation of dimers of Aβ-(1–40) at low micromolar concentrations. Whether this switch occurs primarily in free monomers or in dimers or whether dimers formed in one Aβ molecule can go on to induce the same switch in other Aβ molecules remains to be investigated. The random incorporation of Aβ-(1–40) and Aβ-(1–40) Met-35(O) in homo- and heterodimers indicates that oxidation of Met-35 is of little or no importance in the formation of dimers. This is also consistent...
Finally, the results also demonstrate the applicability of electrospray ionization mass spectrometry to the study of the formation of small amyloid peptide aggregates and their kinetics in the nanomolar to micromolar range. Larger aggregates (decamers or larger) of Aβ peptides should be possible to detect in mass spectrometers of this type if present in micromolar concentrations (22), provided they survive the transition from liquid to gas phase and provided that stable electrospray conditions can be obtained in such solutions.

In conclusion, we believe these results emphasize the need for more detailed molecular and mechanistic knowledge of the complex multistep Aβ fibrillation reaction to rapidly provide a more profound understanding of both cause and effect of Aβ-mediated actions in vitro and also in vivo. In addition, the post-translational Met-35 modification, if it is effectuated in vivo, provides an intriguing possibility for the brain involving rerouting Aβ from a potential protofibrillar/fibrillar pathway to a pathway that opens up better prospects of keeping low molecular weight Aβ species in solution longer, thereby increasing the likelihood of proteolysis and clearance while decreasing the risks of deposition. The growing scientific foundation for a role in vivo can be obtained in such solutions.

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