Certain Metals Trigger Fibrillation of Methionine-oxidized α-Synuclein*

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The aggregation and fibrillation of α-synuclein has been implicated as a key step in the etiology of Parkinson’s disease and several other neurodegenerative disorders. In addition, oxidative stress and certain environmental factors, including metals, are believed to play an important role in Parkinson’s disease. Previously, we have shown that methionine-oxidized human α-synuclein does not fibrillate and also inhibits fibrillation of unmodified α-synuclein (Uversky, V. N., Yamin, G., Souillac, P. O., Goers, J., Glaser, C. B., and Fink, A. L. (2002) FEBS Lett. 517, 239–244). Using dynamic light scattering, we show that the inhibition results from stabilization of the monomeric form of Met-oxidized α-synuclein. We have now examined the effect of several metals on the structural properties of methionine-oxidized human α-synuclein and its propensity to fibrillate. The presence of metals induced partial folding of both oxidized and non-oxidized α-synucleins, which are intrinsically unstructured under conditions of neutral pH. Although the fibrillation of α-synuclein was completely inhibited by methionine oxidation, the presence of certain metals (Ti^{3+}, Zn^{2+}, Al^{3+}, and Pb^{2+}) overcame this inhibition. These findings indicate that a combination of oxidative stress and environmental metal pollution could play an important role in triggering the fibrillation of α-synuclein and thus possibly Parkinson’s disease.

Parkinson’s disease (PD)1 is the second most common neurodegenerative disorder after Alzheimer’s disease. Clinical symptoms of PD (tremor, rigidity, and bradykinesia) are attributed to the progressive loss of dopaminergic neurons from the substantia nigra. Some surviving nigral dopaminergic neurons contain cytosolic filamentous inclusions known as Lewy bodies and Lewy neurites (1, 2), a major fibrillar component of which contain cytosolic filamentous inclusions known as Lewy bodies (11, 13–18). Fibrillation occurs via a nucleation-dependent polymerization mechanism (14, 17) with a critical initial structural transformation from unstructured to partially folded intermediate (11).

The cause of PD is unknown, but considerable evidence suggests a multifactorial etiology involving genetic susceptibility and environmental factors. Recent work has shown that, except in extremely rare cases, there appears to be no direct genetic basis of PD (19). However, several studies have implicated environmental factors, especially pesticides and metals (20). In agreement with these observations, it has been recently reported that direct interaction of α-synuclein with metal ions (21) or pesticides leads to accelerated fibrillation (22–24).

Oxidative injury is also suspected as another causative agent in the pathogenesis of PD (25, 26). The existence of nitrated α-synuclein (i.e. protein containing the product of the tyrosine oxidation, 3-nitrotyrosine) accumulation in Lewy bodies has been demonstrated (27–29). Accumulation of another product of tyrosine oxidation, dityrosine, has been detected in vitro during experiments on the aggregation of α-synuclein in the presence of copper and H₂O₂ (30) or catecholamines (31) and leads to accelerated fibrillation of α-synuclein (32). The methionine side chain is the most readily oxidized amino acid in α-synuclein, and the four methionines, Met-1, Met-5, Met-116, and Met-127, are easily oxidized in vitro in the presence of H₂O₂. Interestingly, however, oxidation of the methionine residues of α-synuclein to the sulfoxides, rather than accelerating fibrillation, was found to prevent it (33). Furthermore, and most importantly, the presence of the methionine-oxidized α-synuclein was found to completely inhibit fibrillation of the unmodified protein at ratios of ~3:1 (33). Given the potential role of metals in the pathological aggregation of α-synuclein and the known strong coordination of some metals to sulfoxides, we decided to investigate the structural and fibrillation properties of Met-oxidized α-synuclein in the presence of several metals to shed more light on the combined effect of environmental factors (metals) and oxidative damage (methionine oxidation to the sulfoxide) on α-synuclein.

MATERIALS AND METHODS

Expression and Purification of Human α-Synuclein—Human recombinant α-synuclein was expressed in the Escherichia coli BL21(DE3) cell line transfected with pPR1722-α-synuclein wild-type plasmid (kind gift of M. Goedert, MBC Cambridge) and purified as described previously (33). Purity of the α-synuclein was determined by SDS-polyacryl-
amide gel electrophoresis, UV absorbance spectroscopy, and mass spectrometry. 

**Supplies and Chemicals**—Thioflavin T (ThT) was obtained from Sigma. ZnSO₄ and CaCl₂ (analytical grade) were from Fisher. Analytical grade Ti₂(SO₄)₃, CuCl₂, and Hg(CH₃CO₂)₂ were from Aldrich, whereas AlCl₃ and PbO₂ were from Mallinckrodt Chemical Works and Matheson Coleman & Bell, respectively. All other chemicals were of analytical grade from Fisher. All buffers and solutions were prepared with nanopure water and stored in plastic vials.

**Oxidation of α-Synuclein by Hydrogen Peroxide**—Oxidation of α-synuclein by H₂O₂ was performed as described previously (33).

**Circular Dichroism (CD) Measurements**—CD spectra were recorded on an AVIV 6DS spectrophotometer (Lakewood, NJ) using α-synuclein concentrations of 1.0 mg/ml and a 0.1-mm path length cell. Spectra were recorded from 250–190 nm with a step size of 1.0 nm, with a bandwidth of 1.5 nm and an averaging time of 10 s. For all spectra, an average of five scans was obtained. CD spectra of the appropriate buffers were recorded and subtracted from the protein spectra.

**Electron Microscopy**—Transmission electron micrographs were collected using a JEOL JEM-100B microscope operating with an accelerating voltage of 80 kV. Typical nominal magnifications were ×75,000. Samples were deposited on Formvar-coated 300-mesh copper grids and negatively stained with 1% aqueous uranyl acetate.

**Fibril Formation Assay**—Fibril formation of oxidized and non-oxidized α-synuclein in the presence of various metals was monitored using the ThT assay in a fluorescence plate reader (Fluoroskan Ascent) as described previously (33). Standard conditions were 35 μM α-synuclein, pH 7.5, 20 mM Tris-HCl buffer, 37 °C, with agitation. ThT fluorescence was excited at 450 nm, and the emission wavelength was 482 nm.

**Estimation of Hydrodynamic Dimensions**—Dynamic light scattering was used to determine the Stokes radii with a DynaPro Molecular Sizing Instrument (Protein Solutions, Lakewood, NJ) using a 1.5-mm path length 12-μl quartz cuvette. Prior to measurement, solutions were filtered with a 0.1-μm Whatman Anodisc-13 filter.

**RESULTS**

**The Effect of Methionine Oxidation and Metal Binding on α-Synuclein Conformation**—We first examined the effect of methionine oxidation on the conformation of α-synuclein and then the effects of selected metals on the conformation of unmodified and Met-oxidized α-synuclein. Fig. 1 compares far-UV CD spectra measured for the non-oxidized (A) and oxidized α-synuclein (B) are shown. CD spectra were measured at pH 7.5 in the absence (filled circles, solid lines) or presence of 5 mM of several metal cations: Al³⁺ (open circles, dotted lines); Zn²⁺ (filled squares, short dashed lines); Cu²⁺ (inverted open triangles, dotted-dashed lines) and Ca²⁺ (inverted filled triangles, long dashed lines). Measurements were carried out at 23 °C in 20 mM Tris-HCl buffer, pH 7.5. Protein concentration was 0.5 mg/ml.
Previously, we demonstrated that the interaction of metal cations with natively unfolded α-synuclein induced a partially folded conformation (21). This transition was attributed to the counter ion-induced neutralization of the coulombic charge-charge repulsion within the very negatively charged protein at neutral pH (21). In agreement with this observation, Fig. 1 shows that in the presence of metals, definite changes occur in the far-UV CD spectra of both non-oxidized and oxidized forms of α-synuclein. In particular, a decrease in the minimum at 196 nm was accompanied by an increase in negative intensity around 222 nm, reflecting metal binding-induced formation of secondary structure (Fig. 1). Significantly, Fig. 1 shows that binding of the metals induced comparable structural changes in both oxidized and unmodified proteins, most probably reflecting the stabilization of identical partially folded conformations. Thus, Met-oxidized α-synuclein is slightly more unfolded than non-oxidized protein, but in the presence of metal ions, it adopts a similar partially folded conformation. Our previous studies have shown that formation of such a partially folded conformation correlates with accelerated fibrillation, as is seen with the effect of metals on non-oxidized α-synuclein (21).

The Effect of Metal Binding on Fibrillation of Methionine-oxidized α-Synuclein—Next, we determined the effect of the metals on the fibrillation of Met-oxidized α-synuclein. ThT is a fluorescent dye that interacts with amyloid fibrils, leading to an increase in the fluorescence intensity in the vicinity of 480 nm (34). Fig. 2 compares fibrillation patterns of non-oxidized (Fig. 2A) and oxidized α-synuclein (Fig. 2B) in the absence and presence of several metal cations monitored by ThT fluorescence. Fibril formation for the non-oxidized α-synuclein at neutral pH was characterized by a typical sigmoidal curve. In agreement with earlier studies (24), the fibrillation rate increased dramatically in the presence of all metal cations investigated (Fig. 2A). The list of the previously analyzed cations (Li⁺, K⁺, Na⁺, Cs⁺, Ca²⁺, Co²⁺, Cd²⁺, Cu²⁺, Fe²⁺, Mg²⁺, Mn²⁺, Zn²⁺, Co³⁺, Al³⁺, and Fe³⁺) has been extended to consider the effect of Hg²⁺, Pb²⁺, and Ti³⁺. Interestingly, Hg²⁺ and Pb²⁺, which are of particular relevance to environment-induced Parkinsonism, are among the most effective accelerators of α-synuclein fibrillation. This underlines, once again, a potential link between heavy metal exposure, enhanced α-synuclein fibrillation, and Parkinson’s disease.

In contrast, there was no evidence of fibril formation by methionine-oxidized α-synuclein at neutral pH (Fig. 2B).

![Fig. 2. Kinetics of fibrillation of non-oxidized (A) and oxidized (B) α-synuclein monitored by the enhancement of thioflavin T fluorescence intensity. Measurements were performed at 37 °C in the absence of metals (black circles) or in the presence of Ti³⁺ (open circles), Zn²⁺ (black triangles), Pb²⁺ (open triangles), Hg²⁺ (black squares), Cu²⁺ (open squares), Ca²⁺ (black diamonds), and Al³⁺ (open diamonds). Solutions contained 5 mM metal salts except for the Ti³⁺, where the concentration was decreased to 0.1 mM due to the low solubility. Measurements were carried out in 20 mM Tris-HCl buffer, pH 7.5. Protein concentration was 0.5 mg/ml. ThT fluorescence was excited at 450 nm, and the emission wavelength was 482 nm.](http://www.jbc.org/Downloaded_from)
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The effect of metal cations on the fibrillation of methionine-oxidized α-synuclein

Kinetic parameters of non-oxidized and oxidized α-synuclein fibrillation in the presence of different metal cations, monitored by ThT fluorescence. Typical errors (S.D.) were 15% on the lag times and 20% on the rate constants. Conditions were 35 μM α-synuclein, pH 7.5, 20 mM Tris-HCl buffer, 37 °C, with agitation.

| Conditions          | Non-oxidized α-synuclein | Oxidized α-synuclein |
|---------------------|--------------------------|-----------------------|
|                     | Lag time | K<sub>app</sub> | t<sub>1/2</sub> | Lag time | K<sub>app</sub> | t<sub>1/2</sub> |
| Control<sup>a</sup> | 18.8     | 0.054    | 55.7  | >200     | ND<sup>b</sup> | ND  |
| 0.1 mM Ti<sub>3</sub>(SO<sub>4</sub>)<sub>3</sub> | 11.1     | 0.092    | 32.8  | 74.8     | 0.081    | 99.6 |
| 5 mM ZnSO<sub>4</sub> | 1.5      | 0.22     | 10.5  | 2.2      | 0.28     | 9.4  |
| 5 mM PbO<sub>2</sub> | 0.3      | 0.46     | 4.6   | 0.9      | 0.41     | 5.8  |
| 5 mM Hg(CH<sub>3</sub>CO<sub>2</sub>)<sub>2</sub> | 3.6      | 0.17     | 15.2  | >200     | ND       | ND  |
| 5 mM CuCl<sub>2</sub> | 12.5     | 0.13     | 28.1  | >200     | ND       | ND  |
| 5 mM AlCl<sub>3</sub> | 21.3     | 0.095    | 42.2  | >200     | ND       | ND  |
| 5 mM TiCl<sub>3</sub> | 10.2     | 0.23     | 18.8  | 24.6     | 0.17     | 36.3 |

<sup>a</sup> All solutions contained 50 mM NaCl.
<sup>b</sup> ND, not determined.

Previously, we showed that inhibitory effect of methionine oxidation on α-synuclein fibrillation can be eliminated under conditions of low pH, due to the formation of a partially folded intermediate reflecting protonation of the carboxylate groups (33). In view of this observation, and the observation that metal cations induce partial folding of oxidized α-synuclein (Fig. 1), one might expect that fibrillation of the methionine-oxidized protein would occur in the presence of metals. In accord with this hypothesis, methionine-oxidized α-synuclein readily formed fibrils in the presence of certain metal ions, such as Ti<sup>3+</sup>, Al<sup>3+</sup>, Zn<sup>2+</sup>, and Pb<sup>2+</sup> (Fig. 2B and Table I). However, not all metals were able to accelerate the fibrillation of methionine-oxidized α-synuclein: for example, Hg<sup>2+</sup>, Cu<sup>2+</sup>, and Ca<sup>2+</sup>, although able to induce the partially folded conformation in the oxidized protein, did not induce its fibril formation (at least not within the time scale examined). Moreover, Fig. 2 and Table I show that in the presence of Zn<sup>2+</sup> and Pb<sup>2+</sup>, fibrillation of the oxidized α-synuclein was as accelerated as for the non-oxidized protein, whereas Al<sup>3+</sup> and Ti<sup>3+</sup> showed a less pronounced effect. The morphology of the fibrillar material formed by the non-oxidized and oxidized α-synuclein in the presence of several metal cations was analyzed by transmission electron microscopy, and both forms of α-synuclein formed typical amyloid fibrils, as shown in Fig. 3.

**Dynamic Light Scattering Experiments to Monitor Hydrodynamic Size**—There are a number of possible mechanisms whereby methionine oxidation could inhibit α-synuclein fibrillation. One of these would be through stabilization of off-pathway oligomers, and another would be through the capping nascent fibrils. To investigate these possibilities, we monitored the association state of Met-oxidized α-synuclein during its incubation, in the absence and presence of metal ions, using dynamic light scattering (Fig. 4). Given the nature of the experimental measurements, populations of oligomers of less than 5–10% are not considered significant. Since the data shown in Fig. 4 are only for soluble protein, the total concentrations may be different in the different panels of the figure.

Met-oxidized α-synuclein remained monomeric for >100 h under standard incubation conditions (35 μM α-synuclein, pH 7.5, 37 °C, with agitation), as shown in Fig. 4D, indicating that neither oligomers nor fibrils were formed in statistically significant amounts. In contrast, unmodified α-synuclein remained predominantly monomeric for the first 20 h (corresponding to the lag time) but then showed dimers and higher oligomers at longer times (in addition to fibrils), as shown in Fig. 4A. Thus, the conversion of methionine to its sulfoxide must, in some way, prevent formation of the critical partially folded intermediate conformation and subsequent association into fibrils.

In the presence of Zn<sup>2+</sup>, which leads to fibril formation from the

**DISCUSSION**

Oxidative stress is believed to be a factor in the etiology of Parkinson’s disease, and the methionine residues of α-synuclein are the most easily oxidized side chains in the protein. Therefore, our previous discovery that methionine-oxidized α-synuclein, which is expected to represent one of the most common products of oxidative damage to α-synuclein, fails to form fibrils and inhibits fibrillation of unmodified α-synuclein was rather surprising, although oxidation of the single methionine residue in Aβ has also been shown to attenuate fibrillation of Aβ (35).

Previously, we have shown that formation of a partially folded intermediate is a critical initial step of the α-synuclein fibrillogenesis (11) and that α-synuclein fibrillation is acceler-
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Figure 4. Population of oligomers during α-synuclein fibrillation determined from dynamic light scattering. Top row, unmodified α-synuclein: control (A), Ca\(^{2+}\) (B), Zn\(^{2+}\) (C). Bottom row, corresponding methionine-oxidized α-synuclein: control (D), Ca\(^{2+}\) (E), Zn\(^{2+}\) (F). The height of the bars represents the population of the species, and the position of the bars reflects the time of incubation and size of the species.

It is becoming clear that many factors can affect the rate of α-synuclein fibrillation, suggesting that in dopaminergic neurons, there is a balance between factors that can accelerate fibrillation and those that inhibit or prevent it. It is likely that there are chaperones or chaperone-like species that are important in minimizing α-synuclein aggregation under normal conditions. In our earlier study, showing that the addition of Met-oxidized α-synuclein inhibited fibrillation of the non-oxidized form (33), we suggested that the methionine residues in α-synuclein may be used by the cells as a natural scavenger of reactive oxygen species, since (a) methionine can react with essentially all of the known oxidants found in normal and pathological tissues; (b) α-synuclein is a very abundant brain protein; (c) it has recently been shown that the concentration of α-synuclein could be increased significantly as a result of the neuronal response to toxic insult (23); and (d) methionine sulf oxide residues in proteins can be cycled back to their native forms by methionine sulfoxide reductase (38), a process that might protect other functionally essential residues from oxidative damage (39). It should be noted, however, that the efficiency of this regeneration system must take into account the finding that methionine oxidation forms the sulfoxide in two diastereoisomer forms and that stereoselective oxidation can sometimes occur, dependent on both the structural restraints in the region of the methionine molecule and on the oxidant itself (40). Each methionine sulfoxide isomer can be...
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reduced back to its original methionine state, provided that
the corresponding complementary redoxase is present and
active (41).

The balance between the protective antioxidant role of
the methionine residues that is enhanced by this recycling and
the toxic insult-induced up-regulation of α-synuclein may no
longer play a protective role; rather, it may represent a risk
factor, leading to metal-triggered fibrillation of the methionine-oxi-
dized protein.

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