A Broken α-Helix in Folded α-Synuclein*

Received for publication, December 23, 2002, and in revised form, February 11, 2003
Published, JBC Papers in Press, February 13, 2003, DOI 10.1074/jbc.M213128200

Sreeganga Chandra‡§*, Xiaocheng Chen∥, Josep Rizo∥, Reinhard Jahn‡§, and Thomas C. Südhof†¶

From the ‡Center for Basic Neuroscience, Department of Molecular Genetics, and Howard Hughes Medical Institute, and the §Departments of Biochemistry and Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9111, and the ¶Max-Planck-Institut für Biophysikalische Chemie, 37075 Göttingen, Germany

α-Synuclein is a small cytosolic protein of presynaptic nerve terminals composed of seven 11-residue repeats and a hydrophilic tail. α-Synuclein misfolding and dysfunction may contribute to the pathogenesis of Parkinson's disease and neurodegenerative diseases (1–3). Two independent mutations in human α-synuclein cause familial Parkinson's disease, and wild-type α-synuclein is a major component of Lewy bodies, cytoplasmic inclusion bodies found in Parkinson's disease and in several forms of neurodegenerative dementia. However, independent of its role in neurodegenerative diseases, α-synuclein is an interesting protein in its own right. It is an abundant presynaptic protein that may regulate neurotransmitter release and may contribute to synaptic plasticity (4–6).

In recent years, the presynaptic protein α-synuclein has attracted much attention because of its involvement in neurodegenerative diseases (1–3). Two independent mutations in human α-synuclein cause familial Parkinson's disease, and wild-type α-synuclein is a major component of Lewy bodies, cytoplasmic inclusion bodies found in Parkinson's disease and in several forms of neurodegenerative dementia. However, independent of its role in neurodegenerative diseases, α-synuclein is an interesting protein in its own right. It is an abundant presynaptic protein that may regulate neurotransmitter release and may contribute to synaptic plasticity (4–6).

α-Synuclein is the founding member of a protein family that additionally includes β- and γ-synucleins and synoretin (7–9). The sequences of all synucleins are similar, although only α-synuclein is implicated in disease. Synucleins are composed of six copies (β-synuclein) or seven copies (all other synucleins) of an unusual 11-residue imperfect repeat, followed by a variable short hydrophilic tail. Synucleins are soluble, natively unfolded proteins that avidly bind to negatively charged phospholipid membranes and become α-helical upon binding (10).

Although secondary structure predictions indicate that the synuclein repeat could form an amphipathic structure consistent with lipid binding, the α-helical conformation is puzzling because the synuclein repeat is punctuated by central glycine residues. Furthermore, in Lewy bodies α-synuclein is thought to be in a β-strand aggregate, but aggregation of α-synuclein into dimers and multimers is promoted by lipid environments that induce an α-helical conformation (11–13). In the present study, we have examined the conformation of α-synuclein in lipidic environments to understand the relation of its sequence to its physicochemical properties and to map a potential pathway of misfolding in neurodegenerative disease.

EXPERIMENTAL PROCEDURES

Production of α-Synuclein—Recombinant α-synuclein was expressed in bacteria as GST-fusion proteins with a TEV protease recognition sequence preceding the N-terminal methionine and cleaved with TEV protease (Invitrogen), resulting in a single additional glycine residue at the N terminus. After TEV cleavage, α-synuclein was isolated as the only heat-stable component upon boiling for 15 min, purified by ion-exchange chromatography on a MonoQ column (Amersham Biosciences), and dialyzed against the appropriate experimental buffers. N15 and C13N15 double-labeled α-synuclein were prepared similarly from bacteria grown in minimal M9 media supplemented with N15 NH4Cl and C13D-Glucose (Cambridge Isotope Laboratories).

Antibodies—Antibodies were raised in rabbits against a peptide corresponding to amino acid 2–24 of human α-synuclein (CDVFMKGK-SKAKEGVVAAEKTQG) that was coupled via its N-terminal cysteine to keyhole limpet hemocyanin, and against recombinant α-synuclein expressed in bacteria.

Partial Tryptic Digestion—α-Synuclein (12.8 μM) was incubated for the indicated times at room temperature in the presence of SUVs (280 molar excess; composition: 30% phosphatidylserine/70% phosphatidylcholine or 100% phosphatidylcholine) or SDS (1 mM) in 20 mM Tris-HCl, pH 7.4, with 0.2% (SUVs) or 2% (SDS) trypsin (Sigma). Digestion products were separated on 15.5% Tris-Tricine gels (14) and analyzed by Coomassie Blue staining or immunoblotting.

NMR Spectroscopy—NMR data were acquired at 25 °C on Varian INOVA600 or INOVA800 NMR spectrometers. All NMR experiments were performed with pulsed-field gradient enhanced pulse sequences (15, 16) using HDO/D2O 95:5 as the solvent. Sample conditions for 1H-15N HSQC spectra are indicated in the corresponding figure legends. Backbone assignments were obtained from three-dimensional 1H-15N NOESY- HSQC, TOCSY-HSQC, HCNO, HNCACB, and CBCA/CO/NH experiments acquired on a 0.3 mM sample of α-synuclein dissolved in 20 mM phosphate buffer, pH 7.4, plus 50 mM SDS. The 3D 1H-15N NOESY-HSQC data were also used to analyze secondary structure NOE patterns and search for long-range NOEs.

Miscellaneous—SUVs of 100% brain phosphatidylcholine or 30% phosphatidylserine, 70% brain phosphatidylcholine (all from Avanti Polar Lipids) were made and quantified as described (17). SUVs were confirmed to be unilamellar by electron microscopy. SDS-PAGE and immunoblotting were performed using standard procedures. CD were recorded at 25 °C in a Jasco Model J-720 instrument upgraded to J-715U and equipped with a 6-position peltier cuvette holder. Recordings were made using Hellma Quartz cuvettes (path length 0.1 cm). Spectra were averaged from 10–50 scans of 0.2 nm steps at a rate of 50 nm/min. Edman degradation was carried out using standard procedures.

* This study was supported by grants from the National Institutes of Health (1-R01-NS40057) (to T. C. S.) and the Deutsche Forschungsgemeinschaft (Gottfried-Wilhelm Leibnitz program) (to R. J.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

† To whom correspondence may be addressed. Tel.: 214-648-1876; Fax: 214-648-1879; E-mail: Thomas.Sudhof@UTSouthwestern.edu (to T. S.); or E-mail: Sreeganga.Chandra@UTSouthwestern.edu (to S. C.).

‡ The abbreviations used are: SUV, small unilamellar vesicle; CD, circular dichroism; HSQC, heteronuclear single quantum correlation; NMR, nuclear magnetic resonance; NOE, nuclear Overhauser effect; NOESY, nuclear Overhauser Effect Spectroscopy; TOCSY, total correlation spectroscopy.
RESULTS AND DISCUSSION

Phospholipid-induced Folding of α-Synuclein—Upon addition of SUVs containing 30% phosphatidylserine and 70% phosphatidylcholine, the CD spectrum of purified α-synuclein shifts from a characteristic random coil pattern with a 195 nm minimum to a typical α-helical pattern with 206 and 222 nm minima (Fig. 1A) (10). Thus phosphatidylserine-containing SUVs induce α-synuclein folding (“folding” as used here refers to the adoption of a secondary, but not necessarily tertiary structure). SUVs composed only of phosphatidylcholine caused little change (data not shown). To determine how many lipids are required for α-synuclein folding, we titrated α-synuclein with increasing amounts of SUVs with a precisely known phospholipid content that were confirmed by electron microscopy to be unilamellar. A progressive increase in α-synuclein folding was observed, with apparent saturation of folding at a molar lipid:protein ratio of ~270–300:1 (Fig. 1B). Taking into account that SUVs are composed of phospholipid bilayers, this ratio indicates that binding of each synuclein molecule requires ~140–150 phospholipid molecules.

Detergent-induced α-Synuclein Folding—To examine the conformation of folded α-synuclein, it is necessary to achieve folding in solution. Therefore we used CD spectroscopy to examine a series of detergents for their ability to support α-synuclein folding. Most detergents tested (Nonidet P-40, n-octylglycoside, Thesit, Tween 20, 3-[3-cholamidopropyl]dimethylammonio]-1-propanesulfonic acid, cholic acid, deoxycholic acid, and taurocholic acid) did not induce folding (data not shown). Only lysophosphatidylserine, lysophosphatidic acid (but not lysophosphatidylcholine), and SDS elicited the same CD change in α-synuclein as acidic SUVs (Fig. 2A and data not shown).

Because complexes of α-synuclein with SDS would be particularly useful in characterizing its structure, we tested whether small phospholipid vesicles and SDS induced similar folded states of α-synuclein. Titration of α-synuclein with increasing concentrations of SDS revealed that SDS promotes folding below its critical micellar concentration (7–10 mM), with complete folding at 1 mM SDS for 13.8 μM α-synuclein (Fig. 2B). This result suggests that ~70 SDS molecules are required per α-synuclein molecule for complete folding, a number that approximates the aggregation number for SDS (i.e. the number of SDS molecules per micelle) (18). Thus it is possible that α-synuclein drives the formation of SDS micelles and folds, as in the case of SUVs, on the surface of the micelles.

Folding Results in Partial Protection from Proteolysis—Limited tryptic digestion of α-synuclein revealed that in the presence of saturating concentrations of SUVs containing phosphatidylserine, α-synuclein was partly protected from proteolysis, whereas SUVs lacking phosphatidylserine had no effect (Fig. 3). Similarly, when we added 1 mM SDS, we also observed partial protection from proteolysis, although the precise pattern of protected fragments was different, presumably because SDS affected the digestion. Immunoblotting with site-specific antibodies showed that the protected fragments (−6 kDa, −4 kDa) under both conditions were derived from the N-terminal region of α-synuclein (Fig. 3). We were unable to ascertain the mass of these fragments by matrix-assisted laser desorption ionization time-of-flight experiments due to lipidic contaminants, but analysis by Edman degradation confirmed that the 4–6 kDa fragments correspond to the N terminus of α-synuclein. Judging from their size, we surmised that one of the cleavage sites is probably at lysines 43 or 45. In support of this conclusion, tryptic digestion of mutant α-synuclein that
lacks these lysines did not produce 4-6 kDa protected fragments (data not shown).

**NMR Analysis of Folded α-Synuclein**—To compare unfolded and folded α-synuclein, we acquired \(^1\)H-\(^15\)N HSQC spectra of α-synuclein alone, or of α-synuclein in the presence of either SUVs (30% brain phosphatidylserine/70% phosphatidylcholine) or SDS (Fig. 4). The \(^1\)H-\(^15\)N HSQC spectrum of α-synuclein alone exhibited a dense cluster of cross-peaks over a narrow range, confirming that the protein is unfolded as described previously (19). The number of visible peaks (~50) was less than expected (135), possibly because of aggregation or of fast chemical exchange between amide groups and the solvent. After addition of saturating concentrations of SUVs, many but not all of the α-synuclein cross-peaks disappeared. This loss of cross-peaks presumably occurred because the large size of the SUVs effectively broadened the resonances of the corresponding amide groups of α-synuclein beyond detection. The positions of α-synuclein cross-peaks that remained after binding to SUVs were unchanged from the spectrum of α-synuclein alone (Fig. 4B), showing that these cross-peaks represent amino acids that do not bind lipids and continue to be unfolded and mobile in the presence of SUVs. Consistent with previous results (19), we observed 36 such amino acids that account for a quarter of the total sequence.

The \(^1\)H-\(^15\)N HSQC spectrum of α-synuclein obtained at saturating concentrations of SDS exhibited an increased dispersion compared with that of isolated α-synuclein (Fig. 4C). This result is consistent with the formation of α-helical structure upon micelle binding revealed by CD spectroscopy (Fig. 2). The number of visible cross-peaks also increased in SDS, most likely because SDS disrupts aggregation and/or because the formation of the α-helical conformation protected the amide groups from exchange with the solvent. Interestingly, the strongest cross-peaks observed in the presence of SDS were generally in the same positions as the cross-peaks that remained in the \(^1\)H-\(^15\)N HSQC spectrum of α-synuclein bound to SUVs (Fig. 4D). Thus these cross-peaks correspond to unfolded residues that do not participate in binding to SUVs micelles or to SUVs, supporting the notion that the binding modes and folding of α-synuclein in both environments are analogous.

**Structural Analysis of Folded α-Synuclein**—To study the structure of α-synuclein bound to SDS, we assigned its backbone signals using triple resonance and three-dimensional \(^1\)H-\(^15\)N NOESY-HSQC and TOCSY-HSQC experiments (Fig. 5). Although a complete analysis of short range NOEs that are diagnostic for different types of secondary structure was made difficult by the strong resonance overlap observed, numerous NOEs could be assigned unambiguously. These include multi-
these sequences exhibit abundant dNN(i/H11001) and dhelical pattern was observed around residues 43 and 44, respectively. Significant positive deviations, which are connect diagonal peaks with dNN(i/H9251/H9251/H11001), illustrate dNN(i/H11001) intensities, are represented in Fig. 7 to account for meanings performed for example with the Expasy program suite (us.expasy.org) predict a mixture of a-helices, random coils, and p-strand. However, the NMR results correlate with the partial proteolysis experiments described above, which uncovered N-terminal protected 4 and 6 kDa bands that correspond to the first a-helix (Fig. 3). The observation of this proteolysis pattern in a-synuclein bound to both SUVs and SDS argue that their conformations are analogous. Absence of Folding Intermediates—At non-saturating concentrations of SUVs or SDS, CD spectra of a-synuclein exhibited intermediate molar ellipticities (Fig. 1). Under these conditions, either only a subset of a-synuclein molecules was fully folded or a defined region of all synuclein molecules, such as part of an a-helix, was folded before the other regions. The first model implies that binding of both helical regions is a cooperative all-or-none process, whereas the second model would involve intermediate states containing partial helices. To distinguish between these possibilities, we acquired a H15-N HSQC spectrum of 0.1 mM synuclein at an intermediate SDS concentration (2.8 mM). If partially helical intermediates exist under these conditions, sharp cross-peaks in the positions cor-

Fig. 6. Composite of (F1, F3) strips of a three-dimensional 1H-15N NOESY-HSQC spectrum of SDS-bound a-synuclein illustrating the NOE patterns observed for residues 36–56. Solid lines connect diagonal peaks with dNN(i,i+1) NOEs as well as intraresidue doN(i,i) NOEs with doN(i,i+3) connectivities.

The NOE data show that most of the 100 N-terminal residues, which include the seven 11-residue repeats, adopt an a-helical conformation. Interestingly, a noticeable break in the helical pattern was observed around residues 43 and 44, revealing an interruption of the helical structure in this region. This break in the helix was also apparent from analysis of the deviations of the observed Ca chemical shifts from random coil values (Fig. 8A). Significant positive deviations, which are characteristic of helical structure, were found for most of the N-terminal 98 residues, but the Ca chemical shifts of residues 43 and 44 were close to random coil values. The abundance of glycines in synuclein made analysis of Ha chemical shift deviations from random coil values difficult because the presence of two Ha protons in each glycine introduces uncertainty in the corresponding deviations. However, these data also illustrated the break in the helix (Fig. 8B). This conclusion is based on the negative deviations characteristic of helical structure that are observed for most of the 100 N-terminal residues, whereas residues 43–45 exhibit slightly positive deviations. In the sequences spanning residues 30–42, 60–65, and 82–100, a few Ha deviations are close to zero, and the Ca deviations are relatively small compared with other parts of the molecule, suggesting that there is helix fraying in these residues. However, the Ca deviations are still around 2 ppm or larger, and these sequences exhibit abundant dNN(i,i+1) and doN(i,i+3) NOE patterns. Thus, these sequences adopt predominantly a-helical conformations that may be partially destabilized by the presence of residues with low helical propensity such as glycines and threonines.

The lack of sequential dNN(i,i+1) and short-range NOEs in the 40 C-terminal residues (Fig. 7) clearly shows that this region of the molecule is largely unstructured. This conclusion is further supported by the observation of sharper resonances in this region than in the rest of the molecule (illustrated by the 1H-15N HSQC cross-peaks; Fig. 4D) and by the small Ca and Ha deviations from random coil chemical shifts (Fig. 8; note that some significant deviations from random coil values may be favored by the abundance of prolines in this region). Extensive analysis of NOESY data did not uncover long-range NOEs indicative of tertiary structure, suggesting that the two a-helices do not interact with each other and are formed only at the protein/micelle interface. This conclusion agrees with the moderate chemical shift dispersion observed in SDS-bound a-synuclein, which indicates the presence of a defined secondary structure but is lower than the dispersion usually observed in globular proteins. Deuterium exchange experiments monitored at pH 6.5 by 1H-15N HSQC spectra further reinforced the conclusion that SDS-bound a-synuclein does not have a tertiary structure because all amide groups were largely exchanged with the solvent within the time scale of the first spectrum (30 min; data not shown).

To assess the secondary structure of a-synuclein by an independent approach, we examined the accessibility of each amino acid of a-synuclein to solvent by measuring their exchange cross-peaks with water using three-dimensional 15N NOESY-HSQC and TOCSY-HSQC spectra (summarized in Fig. 7). The intensity of the exchange cross-peaks directly reflects the exposure of the respective amino acid to solvent. We observed strong exchange cross-peaks, which are indicative of a lack of amide protection for the unstructured C-terminal residues consistent with the non-structured nature of the corresponding sequence (see above). Furthermore, exchange cross-peaks were weak or absent for much of the residues in the helical regions as expected. In the region around residues 43–44, however, exchange cross-peaks with intermediate intensity were observed, which confirms the helical break in this region. Overall, the NMR data yield a picture whereby the 100 N-terminal residues of a-synuclein bound to SDS do not form a globular structure but adopt an a-helical conformation with a break in the middle. The discovery of two a-helices in the folded conformation of a-synuclein was unanticipated as secondary structure calculations performed for example with the Expasy program suite (us.expasy.org) predict a mixture of a-helices, random coils, and p-strand. However, the NMR results correlate with the partial proteolysis experiments described above, which uncovered N-terminal protected 4 and 6 kDa bands that correspond to the first a-helix (Fig. 3). The observation of this proteolysis pattern in a-synuclein bound to both SUVs and SDS argues that their conformations are analogous.
resonance overlap. Solvent was observed (closed circles), whereas an intermediate exchange cross-peak intensity indicated partial protection (open circles). Question marks indicate amide groups whose protection could not be assessed due to resonance overlap. Amide groups were considered protected from exchange if no cross-peak or a weak cross-peak with the solvent was observed (open circles) or medium; <0.6, weak. Open boxes indicate dNN(i,i+1) connectivities that cannot be assessed due to resonance overlap. Observed dNN(i,i+3) NOEs are represented by solid lines, whereas dashed lines indicate dNN(i,i+3) NOEs that could not be assessed because of resonance overlap.

The primary sequence of α-synuclein is shown on top, and amide protection data and diagnostic NOE patterns are summarized below the sequence. Amide protection was assessed from the intensities of exchange cross-peaks with the solvent in three-dimensional 1H-15N NOESY-HSQC and TOCSY-HSQC spectra. The intensities were classified in three categories (weak, intermediate, and strong). Amide groups were considered protected from exchange if no cross-peak or a weak cross-peak with the solvent was observed (closed circles), whereas an intermediate exchange cross-peak intensity indicated partial protection (open circles). Question marks indicate amide groups whose protection could not be assessed due to resonance overlap. Solid boxes indicate the observation of dNN(i,i+1) NOEs. The height of the boxes reflects the intensity ratio between dNN(1) and dNN(3) NOEs that could not be assessed because of resonance overlap. Open boxes indicate dNN(i,i+1) connectivities that cannot be assessed due to resonance overlap. Observed dNN(i,i+3) NOEs are represented by solid lines, whereas dashed lines indicate dNN(i,i+3) NOEs that could not be assessed because of resonance overlap.

Conformational shifts of α-synuclein bound to SDS. Plots of the differences between the Ca (A) and Ha (B) chemical shifts observed for α-synuclein in SDS and those expected for a random coil conformation as a function of the residue number. Helical regions are characterized by positive values for ΔCa and negative values for ΔHa. Random coil chemical shifts were obtained from the BioMagResBank. The arrow identifies the break in the α-helix at which the values for ΔCa and ΔHa resemble those of residues in a random coil conformation.

Implications for α-Synuclein Function and Dysfunction—We have shown that SUVs containing phosphatidylserine and SDS induce folding of α-synuclein in a concentration-dependent manner, with saturation at ~140 phospholipid or 70 SDS molecules per α-synuclein molecule. In folded α-synuclein, the

FIG. 8. Conformational shifts of α-synuclein bound to SDS. Plots of the differences between the Ca (A) and Ha (B) chemical shifts observed for α-synuclein in SDS and those expected for a random coil conformation as a function of the residue number. Helical regions are characterized by positive values for ΔCa and negative values for ΔHa. Random coil chemical shifts were obtained from the BioMagResBank. The arrow identifies the break in the α-helix at which the values for ΔCa and ΔHa resemble those of residues in a random coil conformation.

FIG. 9. Primary and secondary structure of synucleins. A, sequence alignment of human synucleins with identification of the eleven-residue repeats and the localization of α-helices. Residues shared among all synucleins are highlighted in black, whereas residues shared among two of the four synucleins are highlighted in gray. The two helices are indicated by solid lines, with the break being denoted by xx. The hatched lines below the alignment show the eleven-residue repeats. B, two-dimensional representation of the three-dimensional conformation of the N-terminal 98 residues of α-synuclein on a helical net. α-Synuclein is shown in a modeled conformation as a single continuous α-helix without a break (left) or in the observed conformation as two α-helices with a two-residue break (right). Hydrophobic residues are shown in blue, charged residues in red, and glycines in green. The N terminus with the initiating methionine is at the bottom and the C terminus on top as indicated.
N-terminal 98 residues are structured, whereas the C-terminal 42 residues retain a random coil configuration. The structured part of α-synuclein forms two distinct α-helices that are interrupted by a two-residue break. Folding appears to be cooperative, without a stable intermediate at non-saturating concentrations of SDS or SUVs. In the folded state, no long-range interactions between α-synuclein residues were observed, suggesting that there is no tertiary structure and that all of the folded residues are directly or indirectly engaged in lipid binding.

The presence of two α-helices in α-synuclein and the position of the break were unexpected. α-Synuclein is composed of seven imperfect repeats composed of 11 residues. These repeats are interrupted after the fourth repeat by a four-residue insertion. The break between the two α-helices occurs in the first half of the fourth repeat, whereas the four-residue inserted sequence is α-helical. Furthermore, the break between the two α-helices consists of only two instead of four residues (Fig. 9A). Thus the break is not caused by the four-residue insertion between repeats; rather, the four-residue insertion serves to maintain the helical structure. When the two α-helices of α-synuclein are analyzed on a helical net, an amphipathic distribution of residues emerges, which explains the avid binding to negatively charged phospholipids (Fig. 9B). However, when the sequence of α-synuclein is modeled into a single α-helix without a break, the orientation of the hydrophobic surface shifts along the α-helix, suggesting that the break between the two helices may allow a more favorable binding of hydrophobic surfaces to the hydrophobic interior of the micelle/membrane. Binding is likely to be stabilized by ionic interactions between positive charged α-synuclein residues and negatively charged phospholipid headgroups because no α-helicity was observed with either membranes or detergents that do not contain negative surface charges. An alternative explanation for the break is that it may facilitate binding of α-synuclein to small vesicles with a high curvature such as synaptic vesicles. If uninterrupted, the α-helix of synuclein would measure 14 nm, which may be too long to coat a highly curved surface.

Our results suggest that α-synuclein may function as a surface-active coat of phospholipid membranes in the presynaptic nerve terminal, possibly of synaptic vesicles (20, 21). Indeed, tryptic digestion of α-synuclein in the presence of synaptic vesicles resulted in protection of N-terminal fragments similar to those seen with phosphatidyserine-containing SUVs (data not shown), indicating that α-synuclein binds to and folds on synaptic vesicles. Alignment of the four human synucleins shows that other synucleins probably adopt a similar secondary structure as α-synuclein (Fig. 9A). The sequences of the two α-helices and of the break are well conserved, whereas the non-folded C termini are not. However, α-synuclein is unique among synucleins because it has a longer second α-helix than β-synuclein, and a more hydrophobic surface than γ-synuclein or synoretin (Fig. 9A). These differences may explain the selective propensity of α-synuclein to aggregate in neurodegenerative diseases. Several recent studies (11–13) have shown that lipidic environments that promote α-synuclein folding also accelerate α-synuclein aggregation, suggesting that the lipid-associated conformation described here may be relevant to α-synuclein misfolding in neurodegenerative diseases.

Acknowledgments—We thank Dirk Fasshauer, Shigeo Takamori, and Wolfram Antonin for help and advice. We also thank Dietmar Riedel for analysis of SUVs by electron microscopy.

REFERENCES
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doi: 10.1074/jbc.M213128200 originally published online February 13, 2003

Access the most updated version of this article at doi: 10.1074/jbc.M213128200

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