α-Synuclein Aggregation and Parkinson’s Disease

Vladimir N. Uversky

Abstract

Parkinson’s disease (PD) is a multifactorial movement disorder in which both genetic and especially environmental factors play important roles. Substantial evidence implicates the aggregation of α-synuclein, an abundant and conservative presynaptic brain protein with unknown function, as a critical factor in PD. Rare familial cases of PD are associated with the mutations A30P (Ala to Pro substitution at position 30), E46K (Glu to Lys substitution at position 46), and A53T (Ala to Thr substitution at position 53) in α-synuclein. The primary structure of α-synuclein is characterized by several unusual motifs, and this protein was shown to have two closely related homologues, β-synuclein and γ-synuclein. Under the physiologic conditions in vitro, α-synuclein is characterized by the lack of rigid well-defined 3-D structure (i.e., it belongs to the class of natively unfolded proteins). Intriguingly, α-synuclein is known to possess remarkable conformational plasticity. The structure of this protein depends dramatically on the environment, and a number of absolutely unrelated conformations have been observed, including a partially folded intermediate that is a key intermediate in aggregation and fibrillation, several oligomeric species, and fibrillar and amorphous aggregates. A number of factors that either accelerate or inhibit the rate of fibrillation in vitro have been described. Accelerators include environmental factors such as certain pesticides and metals, molecular crowding, and various natural and synthetic charged polymers. Inhibitors include high concentrations of stabilizers such as trimethylamine N-oxide (TMAO), certain catechols, rifampicin, baicalein, acidic lipid vesicles, and protein homologues (β- and γ-synucleins). Oxidation of the four methionine residues in α-synuclein leads to the abolishment of fibrillation, as does the nitration of tyrosine residues. There is a strong correlation between the conformation of α-synuclein (induced by various factors) and its rate of fibrillation. The aggregation process appears to be branched, with one pathway leading to fibrils and another to oligomeric intermediates that may ultimately form amorphous deposits. The molecular basis of Parkinson’s disease appears to be tightly coupled to the aggregation of α-synuclein and the factors that affect its conformation.

4.1. Introduction

Although clinical symptoms of Parkinson’s disease (PD) were first described less than 200 years ago (Parkinson, 1817), there are reports of possible parkinsonian syndromes dating back thousands of years (Duvoisin, 1992a; Gourie-Devi et al., 1991). Today, PD is the second most common neurodegenerative disorder after Alzheimer’s disease. It is estimated that ~1.5 million
Americans are affected by PD. Because only a small percentage of patients are diagnosed before age 50, PD is generally considered an aging-related disease, and approximately 1 of every 100 persons over the age of 60 in the United States suffers from this disorder. PD is a slowly progressive disease that affects neurons of the substantia nigra, a small area of cells in the midbrain. Gradual degeneration of the dopaminergic neurons causes a reduction in the dopamine content. This, in turn, can produce one or more of the classic signs of Parkinson’s disease: resting tremor on one (or both) side(s) of the body; generalized slowness of movement (bradykinesia); stiffness of limbs (rigidity); and gait or balance problems (postural dysfunction). The precise mechanisms of neuronal death are unknown as of yet. Some surviving nigral dopaminergic neurons contain cytosolic filamentous inclusions known as Lewy bodies (LBs) when found in the neuronal cell body or Lewy neurites (LNs) when found in axons (Forno, 1996; Lewy, 1912). Abundant LBs and LNs in the cerebral cortex are also neuropathologic hallmarks of dementia with Lewy bodies (DLB), a common late-life dementia that is clinically similar to Alzheimer’s disease, the Lewy body variant of Alzheimer’s disease, the diffuse Lewy body disease, the multiple system atrophy, and the neurodegeneration with brain iron accumulation type I (Arawaka et al., 1998; Gai et al., 1998; Lucking and Brice, 2000; Okazaki et al., 1961; Spillantini et al., 1998a; Spillantini et al., 1997; Takeda et al., 1998; Trojanowski et al., 1998; Wakabayashi et al., 1997; Wakabayashi et al., 1998).

The pathognomonic cellular lesions found in multiple system atrophy are known as glial cytoplasmic inclusions, or GCIs (Forno, 1996; Papp et al., 1989). It has been pointed out that all aforementioned disorders are brain amyloidoses unified by pathologic intracellular inclusions of aggregates having the α-synuclein protein as a key component (Lundvig et al., 2005; Spillantini et al., 1998a; Wakabayashi et al., 1997).

Several observations implicate α-synuclein in the pathogenesis of PD and several other neurodegenerative disorders known as synucleinopathies (Trojanowski and Lee, 2003). Furthermore, it has been emphasized that because of the accumulation of the evidence connecting α-synuclein to mechanisms underlying PD and related neurodegenerative brain amyloidoses, the year 1997 became a turning point in the reassessment of the molecular basis of Parkinson’s disease (Trojanowski, 2003). For example, a direct role for α-synuclein in the neurodegenerative processes in PD and Lewy body dementia is demonstrated by genetic evidence. Autosomal dominant early-onset Parkinson’s disease and Lewy body dementia was shown to be induced in a small number of kindreds as a result of three different missense mutations in the α-synuclein gene, corresponding with Ala to Pro substitution at position 30 (A30P), Glu to Lys substitution at position 46 (E46K), and Ala to Thr substitution at position 53 (A53T) in α-synuclein (Kruger et al., 1998; Polymeropoulos et al., 1997; Zarranz et al., 2004) or as a result of the hyperexpression of the wild-type α-synuclein protein due to gene triplication (Farrer et al., 2004; Singleton et al., 2004; Singleton et al., 2003). Antibodies to α-synuclein detect this protein in LBs and LNs, the hallmark lesions of PD. Therefore, a substantial portion of fibrillar material in these specific inclusions was shown to be comprised of α-synuclein, and insoluble α-synuclein filaments can be recovered from purified LBs (Spillantini et al., 1998b; Spillantini et al., 1997). The production of wild-type (WT) α-synuclein in transgenic mice (Masliah et al., 2000) or of WT, A30P, and A53T in transgenic flies (Feany and Bender, 2000), leads to motor deficits and neuronal inclusions reminiscent of PD. Interestingly, it has been established that the peptide derived from the central hydrophobic region of α-synuclein represents a second major intrinsic constituent of the Alzheimer’s plaques. Under the particular conditions, cells transfected with α-synuclein might develop LB-like inclusions (see Chapter 5). Other important observations correlating α-synuclein and PD pathogenesis, being reviewed in more detail elsewhere (Dev et al., 2003; Dickson, 2001; Goedert, 2001a; Goedert, 2001b; Trojanowski and Lee, 2003; Uversky and Fink, 2002b), are briefly outlined below. By numerous studies from different laboratories, it has been established that the recombinant α-synuclein easily assembles into amyloid-like fibrils in vitro, and this