Conformations and Aggregation of Alzheimer's Disease Peptides Studied by Ion Mobility

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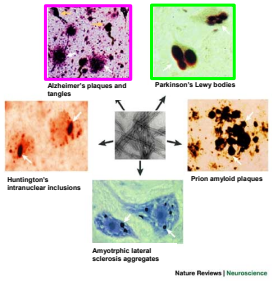
ABSTRACT

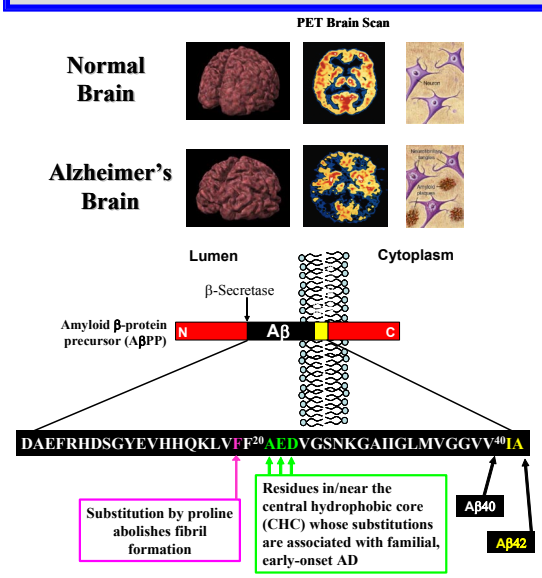
The amyloid beta protein exists in two alloforms: (Aβ40) and (Aβ42). Even though Aβ42 differs from Aβ40 only in two additional C-terminal residues (I and A) it is the primary constituent of Alzheimer's related plaques. Recent studies indicate Aβ42 is highly toxic at nanomolar levels and forms fibrils at a much faster rate than Ab40.[1] Further, current research suggests that the soluble oligomeric forms of Aβ42 are the toxic agents, not the fibrils, and are the major players of neurodegeneration in AD patients.[2] Recent results from Teplow's lab show the mutation Aβ42-F19P abolishes aggregation and fibril formation.[3] Recent work at UCSB indicates that Aβ42(wt) and Aβ42-F19P have very similar mass spectra for the fresh sample but after incubation for 24 hours a large minus 5 charged dimer peak appears in the Aβ42-F19P mass spectrum but not in the Aβ42(wt). The arrival time distribution (ATD) of the -5 dimer is bimodal indicating 2 separate dimer conformations. The more compact species (D_1) has a cross section of over 10% smaller than the more extended conformer (D_2). Above 300K, D_1 begins to dissociate, disappearing by 400K. Near 430K D_2 begins to dissociate near 430K, disappearing near 500K. Comparison with the mass spectrum suggests D_1 may dissociate preferentially although some isomerization to D_2 cannot be excluded. Two dimer conformations in the minus 6 charge state are also observed, in this case for both Aβ42(wt) and Aβ42-F19P. In this instance, D_1 is always significantly smaller than D_2. The ATD also indicates the presence of the minus 3 monomer which grows in relative abundance as either temperature or injection voltage is raised. Analysis of all the data SUGGESTS D_1 closely resemble the solution conformer while D_2 is the favored solvent free conformation. Molecular modeling is yet complete but preliminary structures of the relevant monomer and dimer species have been determined.

1.Barrow CJ & Zagorski MG, *Science* **253** (5016): 179-182 (1991). Jarrett JT et al., *Ann. N. Y. Acad. Sci.* **695**: 144-148 (1993)
2. Bitan et al, *PNAS*, **100** (1): 330-335(2003)
3. Bitan, G. etal in publication

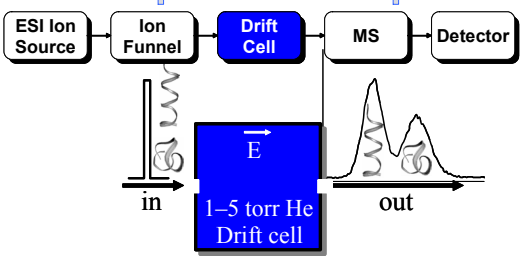
Cerebral Aggregates in Neurodegenerative Diseases



Extracellular amyloid plaques (white arrows) and intracytoplasmic neurofibrillary tangles (yellow arrows) are the pathological signature of Alzheimer's disease. Intracytoplasmic aggregates are typically present in the neurons of people affected by Parkinson's disease and amyotrophic lateral sclerosis. Intranuclear inclusions of huntingtin are observed in Huntington's disease patients and extracellular prion amyloid plaques that are located in different brain regions are present in some cases of transmissible spongiform encephalopathy. In spite of the different protein compositions, the ultrastructure of these deposits seems to be similar and composed mainly of a network of fibrillar polymers (centre).
Soto C NATURE REVIEWS NEUROSCIENCE 4 (1): 49-60 JAN 2003

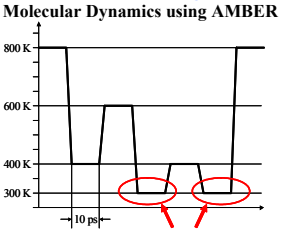


Experimental Setup



Theory

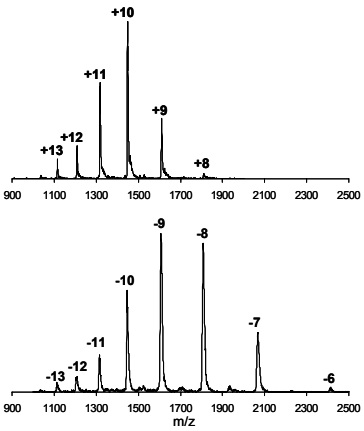
Molecular Dynamics using AMBER

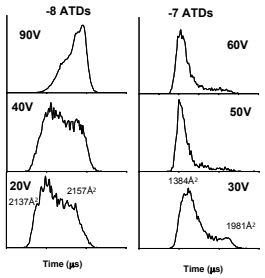


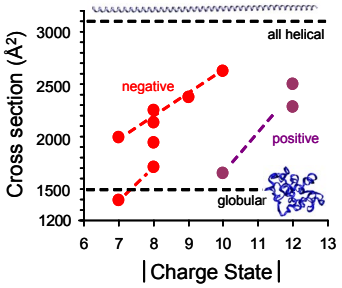
Get 60,000 structures (300 K) & 60,000 cross sections

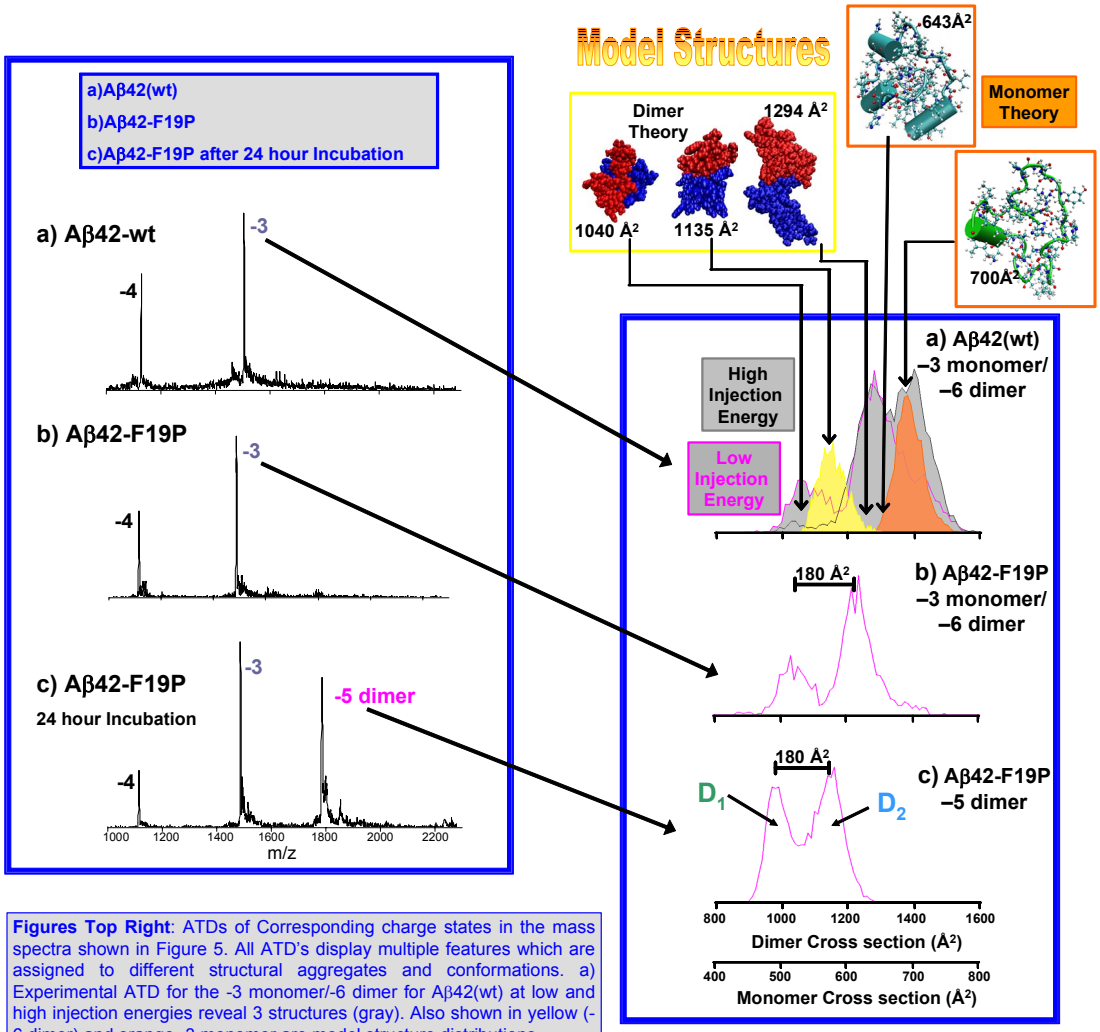
Parkinson's Disease: α-synuclein

Mass Spectra: positive and negative



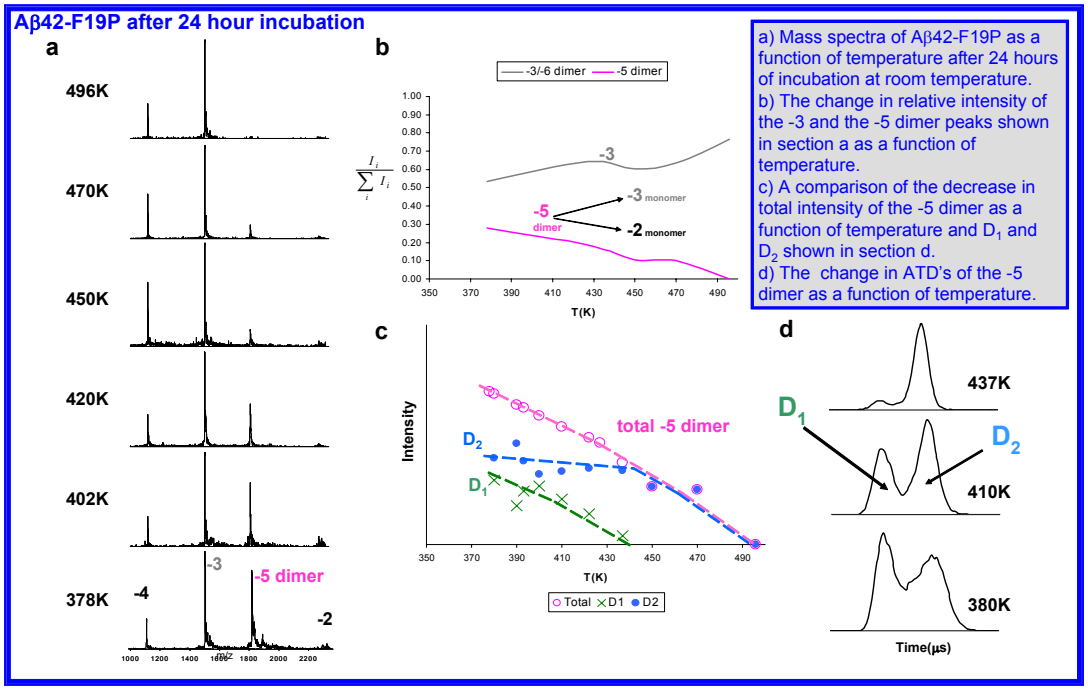






Figures Top Right: ATDs of Corresponding charge states in the mass spectra shown in Figure 5. All ATD's display multiple features which are assigned to different structural aggregates and conformations. a) Experimental ATD for the -3 monomer/-6 dimer for Aβ42(wt) at low and high injection energies reveal 3 structures (gray). Also shown in yellow (-6 dimer) and orange -3 monomer are model structure distributions.

b) ATD for -3 charge state of Aβ42-F19P at low injection energy. c) -5 dimer ATD for Aβ42-F19P which has two features. These two features have the same spacing in cross section as the low injection features seen in the -3 monomer/-6dimer.



a) Mass spectra of Aβ42-F19P as a function of temperature after 24 hours of incubation at room temperature.
b) The change in relative intensity of the -3 and the -5 dimer peaks shown in section a as a function of temperature.
c) A comparison of the decrease in total intensity of the -5 dimer as a function of temperature and D_1 and D_2 shown in section d.
d) The change in ATD's of the -5 dimer as a function of temperature.