Conformation of tau protein, the subunit of Alzheimer paired helical filaments, studied by solution X-ray scattering

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Tau protein is a neuronal microtubule-associated protein. Its main role is to stabilize the microtubules in axons of nerve cells. This in turn enables microtubules to serve as tracks for intracellular transport of cellular cargoes from the cell body to the nerve terminals and back again. Examples are cell organelles (mitochondria, peroxisomes), vesicles containing proteins and lipids (such as synaptic vesicles and other types of vesicles), or protein complexes (e.g. components of receptors). Tau is a highly soluble protein, however, in brain diseases such as Alzheimer's disease tau becomes modified (mainly by phosphorylation at multiple sites) and aggregates into the pathologically "paired helical filaments" that are a hallmark of Alzheimer's and other neurodegenerative "tauopathies". In the adult human central nervous system, tau occurs mainly as 6 isoforms which are generated by alternative splicing from a single gene located on chromosome 17. In previous studies we have investigated the conformation of tau and its aggregation into fibers by biochemical and spectroscopic methods [1]. The results showed that tau is a prototype of a "natively unfolded protein" in which secondary structure elements such as α-helices and β-sheets are nearly absent. Nevertheless, the hydrodynamic behavior of tau shows that its structure is distinct from molten-globule or denatured states [2]. This suggests that there must be elements of folding which are retained in an otherwise "random chain" environment which may be responsible for the functions of tau, such as binding and stabilizing microtubules or the pathological function of aggregation into fibers [3].

In order to determine characteristic features of tau in solution we performed a solution X-ray scattering study. The measured constructs of tau included *ht40*, the largest alternatively spliced form (441aa-containing all exons), *ht23* (the smallest form, 352aa), *K18* (a construct containing the whole repeat domain of tau, 130aa) and *K19,* a construct containing only three of the four repeats, 99aa). The SAXS data were collected on the X33 beamline using a MAR Image Plate detector for solute concentrations 2, 5 and 10 mg/ml and were processed by the program PRIMUS [4]

Radii of gyration of tau constructs in nm (in brackets are the values predicted for a random coil of the given length [5]

K19	(n=99)	RgExp = 3.5 ± 0.1	(2.9)
K18	(n=130)	RgExp = 3.8 ± 0.1	(3.4)
ht23	(n=352)	RgExp = 5.4 ± 0.2	(6.0)
ht40	(n=441)	RgExp = 6.1 ± 0.3	(6.9)

The data obtained thus far reveal two notable features: The observed radii of gyration differ significantly from those expected from a random coil, indicating that the assumption of randomness is not strictly applicable. Secondly, the R_g values of the constructs derived from the repeat domain of tau (K18, K19) are greater than calculated on the basis of a random coil. On the other hand, full-length tau proteins (ht23, ht40) have R_g values smaller than expected, suggesting the existence of some global folding. These observations will be expanded in future experiments in which different combinations of domains will be analyzed.

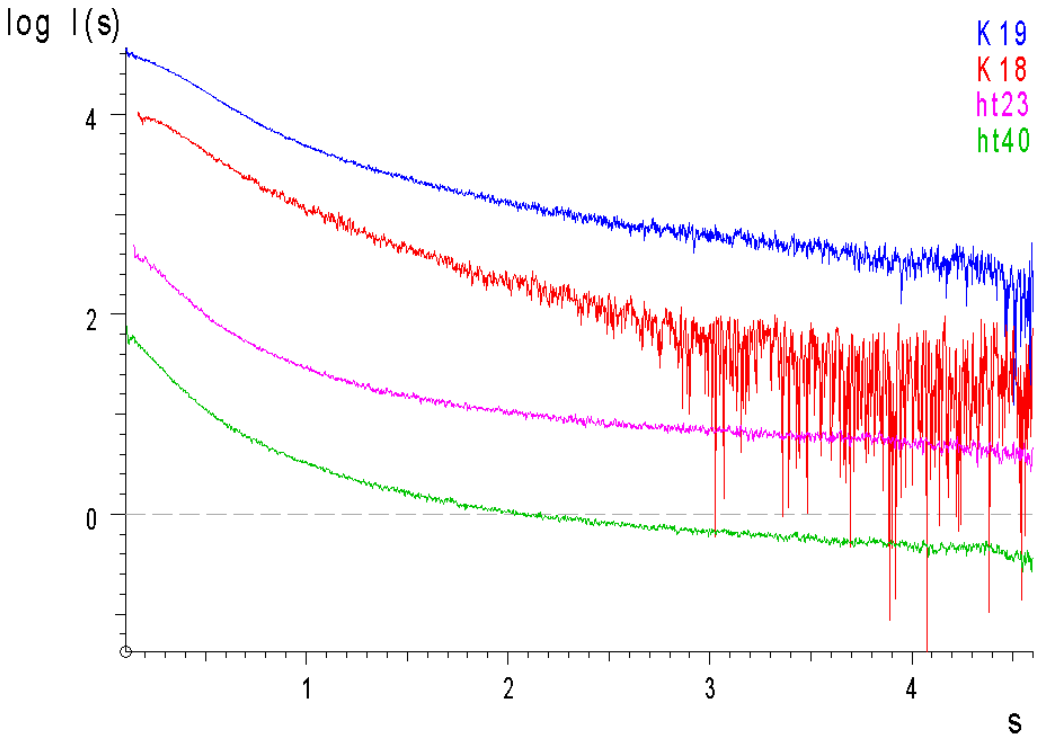

Figure 1: The scattering patterns of human tau. From top to bottom: *K19, K18, ht23, ht40.* The plot displays the logarithm of the scattering intensity as a function of momentum transfer $s=4\pi \sin(\theta/2)/\lambda$ where θ is the scattering angle and $\lambda = 0.15$ nm is the X-ray wavelength. The successive curves are displaced down by one order of magnitude in the logarithmic scale..

References

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