The induction of $\alpha$-helical structure in partially unfolded HypF-N does not affect its aggregation propensity.

The conversion of proteins into structured fibrillar aggregates is a central problem in protein chemistry, biotechnology, biology and medicine. It is generally accepted that aggregation takes place from partially structured states of proteins. However, the role of the residual structure present in such conformational states is not yet understood. In particular, it is not yet clear as to whether the $\alpha$-helical structure represents a productive or counteracting structural element for protein aggregation. We have addressed this issue by studying the aggregation of pH-unfolded HypF-N. It has previously been shown that the two native $\alpha$-helices of HypF-N retain a partial $\alpha$-helical structure in the pH-unfolded state and that these regions are also involved in the formation of the cross-$\beta$ structure of the aggregates. We have introduced mutations in such stretches of the sequence, with the aim of increasing the $\alpha$-helical structure in the key regions of the pH-unfolded state, while minimizing the changes of other factors known to influence protein aggregation, such as hydrophobicity, $\beta$-Sheet propensity, etc. The resulting HypF-N mutants have higher contents of $\alpha$-helical structure at the site(s) of mutation in their pH-unfolded states, but such an increase does not correlate with a change of aggregation rate. The results suggest that stabilisation of $\alpha$-helical structure in amyloidogenic regions of the sequence of highly dynamic states...
does not have remarkable effects on the rate of protein aggregation from such conformational states. Comparison with other protein systems indicate that the effect of increasing \( \beta \)-helical propensity can vary if the stabilised helices are in non-amyloidogenic stretches of initially unstructured peptides (accelerating effect), in amyloidogenic stretches of initially unstructured peptides (no effect) or in amyloidogenic stretches of initially stable helices (decelerating effect).