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Beta-cyclodextrin decreases the aggregation rate of prion proteins induced by metal-catalyzed oxidation

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Prion diseases, also called transmissible spongiform encephalopathies (TSEs), comprise a group of fatal neurodegenerative disorders that affect both humans and animals. Human forms of prion disease include Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), and kuru. Prion diseases affecting animals include scrapie in sheep and goat as well as bovine spongiform encephalopathies (BSE) in cattle. The histopathological features of TSEs such as spongiform degeneration of the brain, neuronal vacuolation, and astrocytic gliosis, represent the main consequences of the cerebral deposition of the misfolding isoform (PrPSc) of the cellular prion protein (PrPC) into amyloid plaques. At present, there is no effective therapy to treate prion diseases. One of the major obstacles in the treatment of TSEs by anti-prion compounds is the low ability of these compounds to cross the blood brain barrier (BBB) that renders their accessibility to the CNS. In addition, most of these compounds did not exhibit any therapeutical effect when administered after the appearance of
neurologic signs into an animal model. Therefore, the development of optimized and effective therapies against TSEs is urgently needed. β-cyclodextrin (β-CD) has been successfully used by the pharmaceutical industry owing to its complex-forming ability. This ability is due to the structural orientation of the glucopyranose units, which generate a hydrophobic cavity that can facilitate the encapsulation of hydrophobic moieties. In this study we investigated the inhibitory effect of β-CD on the in vitro oxidative aggregation of the structured C-terminal domain of both mouse and human prion proteins induced metal catalyzed oxidation (MCO). β-CD gained attention in the field of anti-prion compounds due to its ability to clear PrPSc from infected cell cultures. Small angle X-ray scattering (SAXS) measurements revealed that the delaying effect of β-CD on the structural conversion of human PrP is rather due to the caging of copper ions generated by MCO than to a direct interaction with PrP. Moreover, the observed pathway switch in the presence of β-CD from unspecific denaturation to specific oligomerization strongly supports the theory that aggregation pathways are determined by the population of specific intermediate states. The results obtained in this study provide new insights toward the developing of a lead structure against TSEs.

Summary

Transmissible spongiform encephalopathies (TSE)or prion diseases are a group of fatal neurodegenerative disorders affecting both animal and human. Its characterized by the conversion of the normal PrPC into its infectious PrPSc isoform. up till now there is no cure from the disease as the available anti-prion compounds did not exhibit any therapeutic effect when administered after the appearance of neurologic signs into an animal model. Here we showed that β-cyclodextrin (β-CD) impairs the cell free aggregation of both human and mouse prion proteins-induced by metal catalyzed oxidation via chelation of Cu++ ions. The results are expected to provide new insights into the development of a lead structure against TSE.

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