Evaluation of Prion Protein Interaction with Quinoline Derivatives: Therapeutic Implications

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The Prion Protein (PrP) is the major agent in a group of diseases called Transmissible Spongiform Encephalopathies (TSE) that are neurodegenerative diseases affecting humans and other mammals. These diseases occur when the native cellular PrP (PrP^C), an alpha-helical-rich protein, present mostly in neural cells, is converted into its infectious misfolded isoform, the scrapie PrP. The PrP^{Sc} is rich in beta-sheets and is partially resistant to protease digestion, undergoing aggregation in the central nervous system. The mechanisms of the PrP^C into PrP^{Sc} conversion are still unclear. Some compounds have been already selected in the search to inhibit this pathological conversion. Previous studies showed that antimalarial compounds, such as quinoline and acridine derivatives have an important anti-scrapie activity. In the present work we investigated the interaction of the recombinant murine PrP with new quinoline derivatives through circular dichroism (CD), intrinsic fluorescence and light-scattering (LS) measurements. Moreover we investigated the modulation of prion domains aggregation by these compounds. Our results showed that the full-length recombinant PrP suffers structural changes when complexed with the quinoline derivates. We have also verified that some compounds were able to inhibit or to induce the aggregation of selected prion domains. Therefore, such compounds might be used therapeutically as valuable drugs to prevent the development of prion diseases.

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