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Prion protein interaction with heparin.

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Conversion of cellular PrP (PrP^{C}) into the pathological conformer, PrP^{Sc}, involves contact between both isoforms and probably requires a cellular factor, such as a glycosaminoglycan (GAG). Though direct interaction between PrP and heparin (Hep), little is known about the structural features implicit in this interaction. In the present work, we developed light-scattering, fluorescence and nuclear magnetic resonance spectroscopy measurements in order to provide information on the chemical and physical properties of the murine recombinant PrP ($rPrP^{23-231}$) interaction with low molecular weight heparin (LMWHep) at pH 7.4 and pH 5.0. We found that LMWHep interacts with $rPrP^{23-231}$ inducing its oligomerization/aggregation. Following the binding kinetics and secondary structure content we found that this oligomerization is mostly transient. The interaction of murine PrP with heparin showed to be higher at the acidic pH. After reaching equilibrium, NMR HSQC spectra showed that the prion protein complexed with LMWHeparin has the same general folding of the free protein, with some chemical shifts changes on N and C-terminal amino acids. We also investigated the interaction of Hep with other PrP constructs, lacking portions of the N-terminal domain ($rPrP^{?51-90}$ and $rPrP^{?32-121}$). Heparin did not bind these constructs at pH 7.4 but was able to interact at pH 5.0, indicating that heparin interacts with the octapeptide repeat region at pH 7.4, but can also interact with other regions of the protein (as the C-terminal domain) when the interaction occurs at pH 5.0. In addition, we searched for Hep sulfation groups important for interaction using modified heparins. Heps containing only 6-O-sulfated or 2-O-sufated groups did not alter significantly the PrP secondary structure. On this basis it may be inferred that these two sulfate groups play an important role in prion-heparin interaction.

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