

Metal Ions Bound to Prion Protein Affect its Interaction with Plasminogen Activation System

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ABSTRACT

Prion diseases are a group of neurodegenerative diseases, which can progress rapidly. Previous data have demonstrated that prion protein (PrP) stimulates activation of plasminogen (Plg) by tissue plasminogen activator (tPA). In this study, using spectroscopic method, we aimed to determine whether PrP's role in activating Plg is influenced by metal binding. We also investigated the region in PrP involved in binding to tPA and Plg, and whether PrP in fibrillar form behaves the same way as PrP unbound to any metal ion i.e., apo-PrP. We investigated the effect of recombinant mouse PrP (residues 23-231) refolded with nickel, manganese, copper, and a variant devoid of any metal ions, on tPA-catalyzed Plg activation. Using mutant PrP (H95A, H110A), we also investigated whether histidine residues outside the octarepeat region in PrP, which is known to bind tPA and Plg, are also involved in their binding. We demonstrated that apo-PrP is most effective at stimulating Plg. PrP refolded with nickel or manganese behave similar to apo-PrP, and PrP refolded with copper is least effective. The mutant form of PrP did not stimulate Plg activation to the same degree as apo-PrP indicating that the histidine residues outside the octarepeat region are also involved in binding to tPA and Plg. Similarly, the fibrillar form of PrP was ineffective at stimulating Plg activation. Our data suggest that upon loss of copper specifically, a structural rearrangement of PrP occurs that exposes binding sites to Plg and tPA, enhancing the stimulation of Plg activation.

Keywords: Plasminogen, Tissue Plasminogen Activator (tPA), Plasmin, Plasminogen Regulation, Prion, Prion Disease.
