

P011 Prion protein does not redox-silence Cu^{2+} , but is a sacrificial quencher of hydroxyl radicals.

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Oxidative stress is believed to play a central role in the pathogenesis of prion diseases. The precise physiological function of PrP^{C} remains uncertain; however Cu^{2+} binds to PrP^{C} *in vivo*, suggesting a role for PrP^{C} in copper homeostasis. Here we examine the oxidative processes associated with PrP^{C} and Cu^{2+} . ^1H NMR was used to monitor chemical modifications of PrP fragments. Incubation of PrP fragments with ascorbate and CuCl_2 showed specific metal catalysed oxidation of histidine residues $\text{His}^{96/111}$, and the methionine residues, $\text{Met}^{109/112}$. The octarepeat region protects $\text{His}^{96/111}$ and $\text{Met}^{109/112}$ from oxidation, suggesting that PrP(90-231) might be more prone to chemical modification. We show that $\text{Cu}^{2+/+}$ redox cycling is not 'silenced' by Cu^{2+} binding to PrP, as indicated by H_2O_2 production for full-length PrP. Surprisingly, although detection of Cu^+ indicates that the octarepeat region of PrP is capable of reducing Cu^{2+} even in the absence of ascorbate, H_2O_2 is not generated unless ascorbate is present. Full-length PrP and fragments cause a dramatic reduction in detectable hydroxyl radicals in an ascorbate/ $\text{Cu}^{2+}/\text{O}_2$ system, however levels of H_2O_2 production are unaffected. This suggests that the PrP does not affect levels of hydroxyl radical production via Fenton's cycling, but the radicals cause highly localised chemical modification of PrP^{C} .