

Manganese and Prion Disease

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ABSTRACT

BSE, vCJD, GSS, FFI, Kuru, CWD, scrapie. These strange names describe a group of diseases called prion diseases which are linked together by the idea that an abnormal aggregated protein found at high levels in the brains of victims can act as an infectious agent. This hypothesis has never been proven. Furthermore, most of these diseases occur sporadically or spontaneously with no known cause. Until BSE no one believe that a prion disease could be transmitted to humans and even now there is no concrete evidence showing that vCJD was caused by BSE. Therefore understanding these diseases is desperately in need to an alternative hypothesis to explain how these diseases are caused. The prion protein is a normal cellular protein found at the synapses of all neurones in all vertebrates. Only mammals get prion disease and mammalian prion protein differs to that of other vertebrates in that it contains an octameric repeat sequence rather than a hexameric one. These repeat sequences all contain histidine and are repeated four times. These sequences have been shown to bind copper. Analysing the way in which the repeat region of mammalian prion protein binds copper might help to explain why mammals can get prion disease. The abnormal protein found in the brains of prion diseases is derived from the normal cellular prion protein, differing in a number of ways including aggregation, resistance to proteinase and secondary structure. Recent studies of prion protein from brains of animals with prion disease have shown that the protein has reduced binding of copper. In the brains of animals without the disease the normal prion protein binds three copper atoms per molecule on average. Recent studies have shown that this protein contains increased levels of manganese. Brains of humans with CJD and mice with scrapie have up to ten times the normal level of manganese. This suggests that disturbance of manganese metabolism is an intrinsic characteristic of these diseases. Experiments using recombinant protein have shown that manganese can substitute at the binding site of mammalian prion protein and displace copper. Protein containing manganese is proteinase resistant and shows many of the characteristics of the disease specific protein. Cells grown in the presence of high manganese and low copper also generate prion protein, which is abnormal, with characteristics of the disease specific form. Manganese containing prion protein can stimulate the formation of fibrils of protein from recombinant protein which does not have manganese bound suggesting it has the propensity to propagate its altered conformation. Recent work by Mark Purdey has shown that environmental clusters of sporadic prion disease are associated with low copper and high manganese in the environment. In Slovakia CJD has a higher incidence in those regions with high industrial pollution of manganese. Although there is no evidence currently linking the new prion diseases, BSE and vCJD, with manganese it is an intriguing possibility that industrial pollution high in manganese may either initiate or exacerbate other causative effects which lead to prion diseases in humans and animals. Manganese on its own is unlikely to be a direct cause of prion disease but it is emerging as a possible risk factor for these diseases. Additionally, high brain manganese might become a marker for human prion disease. Simple non-invasive techniques such as MRI might provided a needed diagnostic tool to distinguish prion diseases from other neurodegenerative disease early after onset of symptoms.