

Risk Assessment of Manganese in the Development of Prion Diseases

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ABSTRACT

The Prion protein (PrP) is a normal host coded protein which degradation is altered and accumulates under a protease resistant abnormal form (PrPres) in prion diseases. In the prion hypothesis developed by S. Prusiner, PrPres by itself is the infectious agent, called prion, responsible for fatal neurodegenerative transmissible diseases wellknown now with the development of bovine spongiform encephalopathy (BSE) in Europe. The mechanism of transformation of the normal PrP in the abnormal protease resistant form *in vivo* is unknown. The recent publication by D. Brown and colleagues of a potential role of manganese in the aging of PrP and an acquisition of resistance to degradation has drawn attention to this molecule and some people have evoked an hypothetical role in the development of BSE in UK.

Although the protease resistance described after the aging of a recombinant protein with manganese does not fit with the classical pattern acquired in prion diseases, the notion of an affinity of manganese for PrP and its potential to replace normally fixed copper seems clear. Untill now, none of the approaches used to modify recombinant PrP *in vitro* turned out to generate infectivity and a transmissible prion disease. In order to make a pertinent analyse of the risk linked to manganese in prion diseases we are studying the consequences of manganese on the aging of normal and recombinant PrP before testing for infectivity *in vivo* by inoculation of hamsters and mice. The best biochemical conditions determined will also be used on infectious PrPres to evaluate an hypothetical role of manganese as a cofactor in the development of the prion diseases.

If infectivity is generated from normal PrP, it would be the proof of the reality of the prion hypothesis. If no positive result emerges, this study will contribute to a better definition of the role of environmental elements in the risk assessment of prion diseases.