

## DYSREGULATED ELEMENTAL LOCALIZATION IN SCRAPIE-INFECTED BRAINS

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Bovine spongiform encephalopathy (mad cow disease), sheep scrapie, and human Creutzfeldt-Jakob disease are members of a group of fatal, neurodegenerative diseases called transmissible spongiform encephalopathies (TSEs). Pathology from these diseases occurs in the cerebellum and other brain regions. TSEs are caused by the misfolding of a host cellular protein (PrP<sup>C</sup>) into a pathogenic isoform (PrP<sup>Sc</sup>). The N-terminal region of both PrP isoforms contains metal-binding repeats and PrP misfolding is thought to disturb metal homeostasis in the brain. Likewise, both isoforms of PrP modulate Ca homeostasis in cultured cells; PrP<sup>C</sup> dampens voltage gated Ca channels whereas PrP<sup>Sc</sup> dysregulates them. Other groups have noted TSE-associated changes in the bulk concentrations of biologically active elements however; previous work has not examined the localization of these elements. Since TSE infection profoundly asserts elemental, biochemical and pathological changes on the brain, we hypothesized that TSE infection affects the distribution of metals in the brain. Using X-ray photoelectron emission spectromicroscopy, we examined the brains of infected hamsters and uninfected controls. We identified areas (~20  $\mu$ m) of high calcium concentration in the cerebella of infected, but not uninfected animals. Fe and Co are excluded from these areas, but are enriched on their periphery. Other metals, including Cu, Al and Cr, are also excluded from calcified areas, but without circumferential enrichment. Based on their size and localization, we hypothesize that these lesions represent groups of cells with altered Ca levels due to scrapie infection. Dysregulation of Ca signaling in these cells leads to alterations in the localization of other biologically important elements. These data suggest novel, localized dysregulations in groups of cells in TSE infection, which may contribute to the pathogenesis of disease.

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