Unfolded protein response transcription factor XBP-1 does not influence prion replication or pathogenesis

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The unfolded protein response (UPR) is a conserved adaptive reaction that increases cell survival under endoplasmic reticulum (ER) stress conditions. X-box-binding protein-1 (XBP-1) is a key transcriptional regulator of the UPR that activates genes involved in protein folding, secretion, and degradation to restore ER function. The occurrence of chronic ER stress has been extensively described in neurodegenerative conditions linked to protein misfolding and aggregation. However, the role of the UPR in the CNS has not been addressed directly. Here we describe the generation of a brain-specific XBP-1 conditional KO strain (XBP-1Nes-/-). XBP-1Nes-/- mice are viable and do not develop any spontaneous neurological dysfunction, although ER stress signaling in XBP-1Nes-/- primary neuronal cell cultures was impaired. To assess the function of XBP-1 in pathological conditions involving protein misfolding and ER stress, we infected XBP-1Nes-/- mice with murine prions. To our surprise, the activat