Dysfunction of the PI3K-Akt-GSK-3 pathway is a common feature in cell culture and in vivo models of prion disease.


Abstract

AIMS:

Transmissible spongiform encephalopathies, also called prion diseases, are characterized by the cerebral accumulation of misfolded prion protein (PrPSc) and subsequent neurodegeneration. However, despite considerable research effort, the molecular mechanisms underlying prion-induced neurodegeneration are poorly understood. Here, we explore the hypothesis that prions induce dysfunction of the PI3K/Akt/GSK-3 signalling pathway.

METHODS:

We employed two parallel approaches. Using cell cultures derived from mouse primary neurons and from a human neuronal cell line, we identified common elements that were modified by the neurotoxic fragment of PrP106-126. These studies were then complemented by comparative analyses in a mouse model of prion infection.

RESULTS:

The presence of a polymerized fragment of the prion protein (PrP106-126) or of a prion strain altered PI3K-mediated signalling, as evidenced by Akt inhibition and GSK-3 activation. PI3K activation by the addition of insulin or the expression of a constitutively-active Akt mutant restored normal levels of Akt and GSK-3 activity. These changes were correlated with a reduction in caspase activity and an increase in neuronal survival. Moreover, we found that activation of caspase 3, Erk and GSK-3 are common features of PrP106-126-mediated neurotoxicity in cellular systems and prion infection in the mouse cerebellum, while activation of caspase 12 and JNK was observed in cellular models.

CONCLUSIONS:

Our findings in cell culture and in vivo models of prion disease demonstrate marked alterations to the PI3K/Akt/GSK-3 pathway and suggest that two additional pathways contribute to PrP-induced neurotoxicity as responsible of JNK and Caspase 12 activation.

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