Prions link cholesterol to neurodegeneration

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Prion infection of neurons increases the free cholesterol content in cell membranes. A new study published in the online open access journal *BMC Biology* suggests that disturbances in membrane cholesterol may be the mechanism by which prions cause neurodegeneration and could point to a role for cholesterol in other neurodegenerative diseases.

It is widely believed that prions (protein only infectious material) are the cause of rare progressive neurodegenerative disorders that affect both humans and animals. A prion is an infectious agent made solely of protein. However what is not known is how the prions damage brain cells (neurons).

Dr Clive Bate and colleagues from the Royal Veterinary College in the UK compared the amounts of protein and cholesterol in prion-infected neuronal cell lines and primary cortical neurons with uninfected controls. Protein levels were similar but the amount of total cholesterol (a mixture of free and esterified cholesterol) was significantly higher in the infected cell lines. The cholesterol balance was also affected: the amount of free cholesterol increased but that of cholesterol esters reduced, suggesting that prion infection affects cholesterol regulation.

The team attempted to reproduce the effects of prions on cholesterol levels, by stimulating cholesterol biosynthesis or by adding exogenous cholesterol. Both approaches resulted in increased amounts of cholesterol esters but not of free cholesterol. The free cholesterol is thought to affect the function of the cell membranes and to lead to abnormal activation of phospholipase A2, an enzyme implicated in the

depletion of neurons in prion and Alzheimer's disease.

Studies have recently shown that the controlling cholesterol levels within the brain is critical in limiting the development of neurodegenerative diseases such as Alzheimer's, Parkinson's and prion diseases, multiple sclerosis, and senile dementia. This study now gives far more specific insight into the kind of mechanisms at work. Dr Bate stated: "Our observations raise the possibility that disturbances in membrane cholesterol induced by prions are major triggering events in the neuropathogenesis of prion diseases".

Source: BioMed Central