Prion protein in zinc metabolism and action of amyloid-β oligomers in Alzheimer's disease

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Introduction

The prion protein is probably best known for its role in the transmissible spongiform encephalopathies or prion diseases, such as Creutzfeldt-Jakob disease in humans and bovine spongiform encephalopathy in cattle. In these diseases the normal cellular form of the prion protein (PrP^{C}) undergoes a conformational conversion to the infectious form, PrP^{Sc}. However, understanding the physiological role(s) of PrP^{C} and whether loss of these contribute to disease are critical.

Alzheimer's disease (AD) is the commonest neurodegenerative disease of old age. Currently, there are no drugs available to halt or slow the progression of this devastating disease which is placing a huge burden on patients and carers. AD is characterised by the deposition in the brain of senile plaques that are composed of the amyloid-β peptide (Aβ). Through mechanisms that are poorly understood, Aβ oligomers, fibrils and/or aggregates are toxic to nerve cells.

Regulation of Aβ toxicity by the prion protein

PrP^{C} was recently identified as a high-affinity neuronal receptor for Aβ oligomers. We report that fibrillar Aβ oligomers recognised by the OC antibody, which have been shown to correlate with the onset and severity of AD, bind preferentially to cells and neurons expressing PrP^{C} (Figure 1). The binding of Aβ oligomers to cell surface PrP^{C}, as well as their downstream activation of Fyn kinase, was dependent on the integrity of cholesterol-rich lipid rafts. Fluorescence microscopy and co-localisation with sub-cellular markers revealed that the Aβ oligomers co-internalised with PrP^{C}, accumulated in endosomes and subsequently trafficked to lysosomes. The cell surface binding, internalisation and downstream toxicity of Aβ oligomers was dependent on the transmembrane low density lipoprotein receptor-related protein-1 (LRP1). The binding of Aβ oligomers to cell surface PrP^{C} impaired its ability to inhibit the activity of the β-secretase BACE1 which cleaves the amyloid precursor protein to produce Aβ. The green tea polyphenol (-)-epigallocatechin gallate (EGCG) and the red wine extract resveratrol both re-modelled the fibrillar conformation of Aβ oligomers. The resulting non-fibrillar oligomers displayed significantly reduced binding to PrP^{C}-expressing cells and were no longer cytotoxic. These data indicate that soluble, fibrillar Aβ oligomers bind to PrP^{C} in a conformation-dependent manner and require the integrity of lipid rafts and the transmembrane LRP1 for their cytotoxicity, thus revealing potential targets to alleviate the neurotoxic properties of Aβ oligomers in AD.

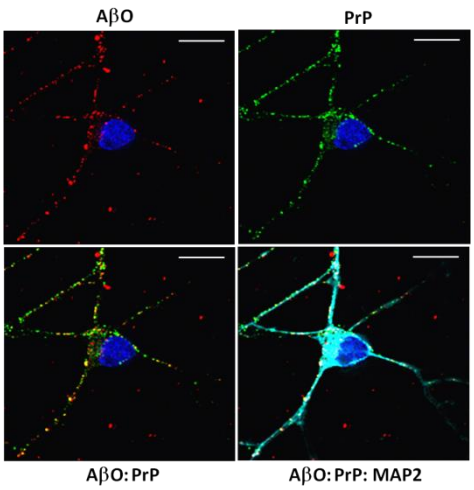

Figure 1: binding of Aβ oligomers (AβO) to rat primary hippocampal neurons expressing PrP^{C} (PrP).

The prion protein facilitates zinc uptake into neurons

Zinc is released into the synaptic cleft upon exocytotic stimuli, although the mechanism for its reuptake into neurons is unresolved. Using zinc specific fluorescent dyes we reported that PrP^{C} enhances the uptake of zinc into neuronal cells. This PrP^{C}-mediated zinc influx required

the octapeptide repeats and N-terminal polybasic region in PrP^C but not its endocytosis. Selective antagonists of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors blocked the PrP^C-mediated zinc uptake and PrP^C co-immunoprecipitated with both GluA1 and GluA2 AMPA receptor subunits. Zinc-sensitive intracellular tyrosine phosphatase activity was decreased in cells expressing PrP^C and increased in the brains of PrP^C null mice, providing evidence of a physiological consequence of the process (Figure 2).

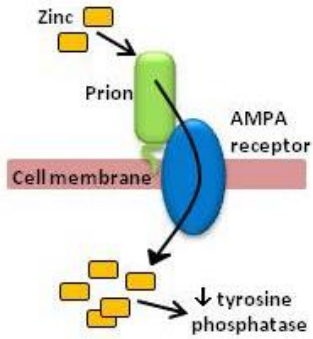

Figure 2: schematic for how PrP^C mediates zinc uptake into cells through AMPA receptors and affects intracellular tyrosine kinase activity.

This PrP^C-mediated zinc uptake was ablated in cells expressing familial prion disease-associated mutants of PrP^C and in prion-infected cells. These data suggest that alterations in PrP^C-mediated zinc uptake may contribute to neurodegeneration in prion and other neurodegenerative diseases.

Publications

Griffiths, H., Whitehouse, I. & Hooper, N. (2012) Regulation of amyloid-beta production by the prion protein. *Prion* **6:**1-6.

Lewis, V., Whitehouse, I., Baybutt, H., Manson, J., Collins, S. & Hooper, N. (2012) Cellular prion protein expression is not regulated by the Alzheimer's amyloid precursor protein intracellular domain. *PLoS ONE* **7:** e31754.

Vardy, E., Kellett, K., Cocklin, S. & Hooper, N. (2012) Alkaline phosphatase is increased in both brain and plasma in Alzheimer's disease. *Neurodegener. Dis.* **9:** 31-37.

Watt, N., Taylor, D., Kerrigan, T., Griffiths, H., Rushworth, J., Whitehouse, I. & Hooper, N. (2012) Prion protein facilitates uptake of zinc into neuronal cells. *Nat. Commun.* **3:** 1134-1134.

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Collaborators

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