Alzheimer’s and prion diseases: cellular and genetic mechanisms of neurodegeneration

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Title of project or programme

Title of PI Alzheimer’s and prion diseases: cellular and genetic mechanisms of neurodegeneration

Principal Investigators of project/programme grant

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- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

1474905.27

Start date of award

01-11-2009

Total duration of award in months

36

The project/programme is most relevant to

- Alzheimer’s disease and other dementias
- Prion disease

Keywords

Research abstract in English

Alzheimers disease (AD) is the major neurodegenerative disease of the aging brain that is extremely complex and poorly understood but which poses an ever-expanding burden on the Health Service and society in an aging population. By contrast the prion diseases, such as Creutzfeldt-Jakob

disease, are relatively rare but have received much attention in recent years because of the potential number of individuals in the UK affected following the epidemic of bovine spongiform encephalopathy. Our working hypothesis is that common molecular and cellular mechanistic features exist between AD and prion diseases. AD is characterised by the deposition in the brain of amyloid-beta peptides that are derived by proteolytic cleavage of the amyloid precursor protein (APP), while prion diseases are characterised by the conformational conversion of the cellular form of the prion protein (PrPC) to the pathogenic form, PrPSc. The overall aim of this proposal is to elucidate further and compare the cellular and genetic regulation of the proteolytic mechanisms and protein-protein interactions that are involved in the normal and pathogenic processing and functions of APP and PrPC. The specific objectives are:

(a) to determine the cellular mechanism by which PrPC inhibits the rate limiting cleavage of APP by the beta-secretase BACE1, and by what mechanism other interacting proteins (that we have identified from the BACE1 and APP interactomes) modulate the cleavage of APP. In addition, we will examine whether key BACE1 and APP interacting proteins are altered in AD and aging, establish if PrPC modulates the gamma-secretase cleavage of APP and determine the mechanism by which the modulation of neurotransmitter receptor signalling increases the alpha-secretase cleavage of APP;

(b) to determine the roles of PrPC endoproteolysis and interacting proteins (some of which are shared with APP) on PrPC function and conversion to PrPSc, and whether PrPC protects against cognitive dysfunction in a mouse model of AD. In addition, we will assess whether localisation of PrPC in different membrane domains modulates its protein interactome;

(c) to investigate the mechanism by which the intracellular domain of APP and histone deacetylase inhibitors may regulate expression of a subset of AD-related genes, especially neprilysin, and to examine if there are global changes in neuronal chromatin in AD and prion disease.

Appreciating the intricacy of the cellular systems will not only advance our understanding of these neurodegenerative disorders but will also help with designing therapeutic interventions as precisely as possible to avoid unintended consequences.

Lay summary
In which category does this research fall?

- Basic research