Altered Heparan Sulfate in Ageing and Dementia: a Potential Axis for Dysregulation of BACE-1 in Alzheimers Disease

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Altered Heparan Sulfate in Ageing and Dementia: a Potential Axis for Dysregulation of BACE-1 in Alzheimers Disease

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€ 117,255

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3

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Research Abstract

Cleavage of amyloid beta-protein precursor (APP) by the enzyme beta-secretase (BACE1) is a key step in A? peptide production and accumulation in brain plaques in AD sufferers. We have discovered that a complex cell sugar called heparan sulphate (HS) inhibits BACE1, providing a new drug discovery target and indicating a possible role as a “brake” on Ab generation in the brain. HS is also known to change in human tissues with ageing and in AD brains, and we have

new preliminary evidence that certain enzymes involved in making HS in cells are present at lower levels in AD.

Our hypothesis is that changes in HS structure during ageing and in dementia may result in taking the “brake” off BACE-1 activity, leading to elevated generation of pathogenic Abeta peptides. We will analyse the structure and BACE-1 inhibitory activity of HS from brains of AD patients and age matched controls, and study expression levels of enzymes which make HS. These studies will help us to understand the in vivo relevance of HS to AD pathogenesis, support targeting HS regulation of BACE1 for development of disease-modifying drugs, and may reveal new genetic or biochemical markers for risk of development of AD.

Further information available at:

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