HERPES SIMPLEX VIRUS TYPE-1 INFECTION INCREASES BACE1 EXPRESSION AND A\textsuperscript{\textbeta} PRODUCTION THROUGH PKR ACTIVATION


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Introduction: Amyloid ß-peptide (A\textbeta) is widely deposited in Alzheimer's disease (AD). BACE1 is the key enzyme involved in the A\textbeta production. Normally, its expression is repressed by a 5'untranslated region (5'UTR) in the BACE1 promoter. This inhibitory effect can be reversed by the phosphorylation of the eukaryotic initiation factor (eIF)2alpha, activating BACE1 expression. There are four known kinases associated with different types of stress that could phosphorylate eIF2alpha. Double-stranded (ds) RNA-activated protein kinase (PKR) can be activated by herpes simplex virus type-1 (HSV1) among other viruses infection. This virus has been linked to AD, acting when present in type 4 allele of the apolipoprotein E gene carriers.

Aims: To demonstrate that HSV1 could activate BACE1 expression through eIF2alpha phosphorylation by PKR.

Methods: Protein expression was studied by western-blot, immunocytochemistry and immunohistochemistry. To study the 5'UTR we performed promoter activity assay with the luciferasa gene.

Results: Here we demonstrate PKR activation by HSV1 infection in neuroblastoma cells and in peripheral nervous tissue. We confirm the 5'UTR inhibitory effect and that it can be prevented by salubrinal, an inhibitor of the eIF2alpha phosphatase PP1c. We also demonstrate that treating HEK-APPsw cells with poly (I:C), dsRNA analog, prevent 5'UTR inhibitory effect, increasing BACE1 expression and A\textbeta production.

Conclusions: Our work suggest an important role of HSV1 in the development of AD by activating PKR pathway, increasing BACE1 expression and A\textbeta production.

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