Amyloid beta peptide increases DP5 expression via activation of neutral sphingomyelinase and JNK in oligodendrocytes.

許重義
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Abstract

There is growing recognition that white matter pathology is a common feature in Alzheimer's disease. We have previously reported that the amyloid beta peptide (Aβ) induces apoptosis in oligodendrocytes (OLG), via activation of neutral sphingomyelinase (nSMase) and resultant generation of ceramide. In the current study, we report that both Aβ and ceramide increased expression of the proapoptotic protein DP5/Hrk (DP5), and release of cytochrome C from mitochondria to cytoplasm in OLGs. We provide evidence that the Jun N-terminal kinase (JNK) signaling pathway mediates Aβ- and ceramide-induced apoptosis: Both Aβ and ceramide activated JNK phosphorylation, and subsequent AP-1 DNA binding activity; JNK siRNA decreased AP-1 DNA binding, DP5 expression and reduced cell death. Furthermore, inhibition of nSMase attenuated Ap-induced JNK phosphorylation, AP-1 DNA binding activity, DP5 expression, and cytochrome C release. Collectively, these results suggest that Ap-induced apoptosis involves the sequential activation of nSMase with ceramide generation, JNK activation, AP-1 DNA binding, and DP5 expression.