

Neutral sphingomyelinase activation in endothelial and glial cell death induced by amyloid beta-peptide.

Yang DI, Yeh CH, Chen S, Xu J, and Hsu CY

Abstract

We have explored the molecular mechanism underlying amyloid beta-peptide (A β)-mediated cytotoxicity in vitro. Exposure of murine cerebral endothelial cells (CECs) or C6 glioma cells to A β ₂₅₋₃₅ resulted in dose-dependent cell death. Ceramide is a pro-apoptotic lipid mediator. Forced elevation of cellular ceramide levels, either by application of an exogenous C2 ceramide analogue or bacterial sphingomyelinase that induces endogenous ceramide release from sphingomyelin, mimicked A β ₂₅₋₃₅ cytotoxicity in both CECs and C6 glioma cells. A β ₂₅₋₃₅-induced synthesis of ceramide was selectively mediated by activation of neutral sphingomyelinase (nSMase), but not acidic sphingomyelinase (aSMase) or ceramide synthase. Both 3-O-Me-SM and N-acetyl-L-cysteine, the selective and nonselective pharmacological inhibitors of nSMase, respectively, suppressed nSMase activation, ceramide production, and cytotoxic action induced by A β ₂₅₋₃₅ in CECs. Furthermore, genetic knockdown of nSMase by an antisense strategy rendered C6 glioma cells specifically resistant to A β ₂₅₋₃₅ cytotoxicity without affecting their vulnerability to serum deprivation. Together, nSMase activation with subsequent ceramide production may contribute, at least partially, to A β ₂₅₋₃₅ cytotoxicity in cell types with cerebral endothelial and glial lineage.