# Amyloid-beta peptide induces oligodendrocyte death by activating the neutral sphingomyelinase-ceramide pathway.

許重義
Lee JT;Xu J;Lee JM;Han X;Yang DI;Chen S;Hsu CY

## Abstract

Amyloid-ß peptide (Aß) accumulation in senile plaques, a pathological hallmark of Alzheimer's disease (AD), has been implicated in neuronal degeneration. We have recently demonstrated that Aß induced oligodendrocyte (OLG) apoptosis, suggesting a role in white matter pathology in AD. Here, we explore the molecular mechanisms involved in Aß-induced OLG death, examining the potential role of ceramide, a known apoptogenic mediator. Both Aß and ceramide induced OLG death. In addition, Aß activated neutral sphingomyelinase (nSMase), but not acidic sphingomyelinase, resulting in increased ceramide generation. Blocking ceramide degradation with N-oleoyl-ethanolamine exacerbated Aß cytotoxicity; and addition of bacterial sphingomyelinase (mimicking cellular nSMase activity) induced OLG death. Furthermore, nSMase inhibition by 3-O-methyl-sphingomyelin or by gene knockdown using antisense oligonucleotides attenuated Aß-induced OLG death. Glutathione (GSH) precursors inhibited Aß activation of nSMase and prevented OLG death, whereas GSH depletors increased nSMase activity and Aß-induced death. These results suggest that Aß induces OLG death by activating the nSMase–ceramide cascade via an oxidative mechanism.