ENDOGENOUS NEUROTOXIN QUINOLINIC ACID MAY PLAY A PRIMARY ROLE IN THE PATHOGENESIS OF AD BY KILLING NEURONS AND INCREASING AMYLOID B PEPTIDES IN THE HIPPOCAMPUS

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Background: Quinolinic acid (QUIN) is an endogenous excitatory neurotoxin which acts through NMDA receptors. A high production of QUIN has been demonstrated in the hippocampus of AD brains. The stimulation of the NMDA receptors, on the other hand, is reported to increase amyloid β peptide (Aβ) levels in cultured neurons, suggesting a pathogenic role of QUIN in AD. We investigated this hypothesis by injecting QUIN into the mouse hippocampus.

Methods: QUIN (40 nmol/1µl) was injected into the hippocampus of mice and the hippocampal Aβ40/42 were assayed by ELISA at 3, 7, 14, 28, and 90 days after injection. Control mice were injected with saline or Glu (40 nmol). Neuronal cell death was examined by Nissl staining.

Results: The levels of Aβs increased gradually and reached a peak (400-500 % of the controls) at 28 days and decreased slowly thereafter. The increase of more toxic Aβ42 was greater than that of Aβ40 throughout the experimental period. These increases were associated with hippocampal neural death, and most neurons disappeared at 28 days. Sever hippocampal atrophy was observed at 90 days. The injection of saline or Glu did not change the Aβ levels.

Conclusions: QUIN was demonstrated to perturb the metabolism of amyloid proteins and increase toxic Aβs. This increase was associated with the loss of neurons and brain atrophy which are pathological characteristics of AD. These findings suggest that QUIN is a primary cause of AD, and the inhibition of QUIN production may be a new therapeutic strategy for AD.