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An amyloid β42-dependent deficit in anandamide mobilization is associated with cognitive dysfunction in Alzheimer's disease

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Abstract

The endocannabinoids and their attending cannabinoid (CB)(1) receptors have been implicated in the control of cognition, but their possible roles in dementias are still unclear. In the present study, we used liquid chromatography/mass spectrometry to conduct an endocannabinoid-targeted lipidomic analysis of postmortem brain samples from 38 Alzheimer's disease (AD) patients and 17 control subjects, matched for age and postmortem interval. The analysis revealed that midfrontal and temporal cortex tissue from AD patients contains, relative to control subjects, significantly lower levels of the endocannabinoid anandamide and its precursor 1-stearoyl, 2-docosahexaenoyl-sn-glycero-phosphoethanolamine-N-arachidonoyl (NArPE). No such difference was observed with the endocannabinoid 2-arachidonoyl-sn-glycerol or 15 additional lipid species. In AD patients, but not in control subjects, statistically detectable positive correlations were found between (1) anandamide content in midfrontal cortex and scores of the Kendrick's Digit Copy test ($p = 0.004$, $r = 0.81$; $n = 10$), which measures speed of information processing; and (2) anandamide content in temporal cortex and scores of the Boston Naming test ($p = 0.027$, $r = 0.52$; $n = 18$), which assesses language facility. Furthermore, anandamide and NArPE levels in midfrontal cortex of the study subjects inversely correlated with levels of the neurotoxic amyloid peptide, amyloid β-protein (Aβ)(42), while showing no association with Aβ(40) levels, amyloid plaque load or tau protein phosphorylation. Finally, high endogenous levels of Aβ(42) in Swedish mutant form of amyloid precursor protein (APP(SWE))/Neuro-2a cells directly reduced anandamide and NArPE concentrations in cells lysates. The results suggest that an Aβ(42)-dependent impairment in brain anandamide mobilization contributes to cognitive dysfunction in AD.

Figures

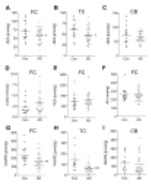

Figure 1 Endocannabinoid-related lipids in midfrontal

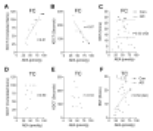

Figure 2 Correlation analyses of anandamide levels...

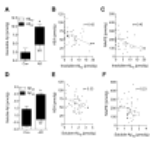

Figure 3 Correlation analyses of Aβ $_{42}$...

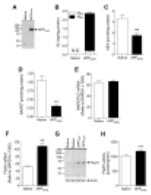

Figure 4 Impaired anandamide production in Neuro-2a...

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