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Title: Reduction of lipid peroxidases levels in EFAD mouse model.

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Abstract:

Background: Cerebral microbleeds (MBs) are more prevalent in APOE4 carriers and associated with Alzheimer Disease (AD). Loss of cerebrovascular integrity, blood-brain barrier breakdown, and reduced Aβ clearance are also shown by APOE4 carrier mice. In AD, increased brain amyloid coupled with increased oxidative stress may synergistically contribute to MBs prevalence.

EFAD mice carrying familial dominant AD genes in combination with human apoE alleles are a model for sex differences in AD, with greater amyloid accumulation and microbleeds in female E4FAD mice.

Independently, Aβ and heme from microbleeds contribute to increased oxidative stress. New data suggest increased lipid peroxidation in E4 mice at baseline as measured by 4-HNE. Peroxiredoxin 6 (Prdx6) and glutathione peroxidase 4 (GPx4) are the only known antioxidant enzymes capable of detoxifying oxidized phospholipids.

Method: Prdx6 and GPx4 were studied by Western blot in cortical lysates of 6mo old EFAD mice. To evaluate Aβ contribution, we analyzed Prdx6 and GPx4 in 2mo old EFAD mice, which show 2 to 10-fold lower Aβ compared to 6mo EFAD mice, and 6mo old EFAD non carrier siblings (no AD-transgene).

Result: Prdx6 was decreased in E4FAD mice (M: -30%; F: -50%) compared to E3FAD mice. GPx4 was decreased only n E4FAD females (M: no change; F: -50%). Younger mice did not show differences in either lipid peroxidases at 2mo. Interestingly, Prdx6 but not GPx4 was reduced in 6mo old female E4FAD non carrier siblings.

Conclusion: Our data suggest that the decreased levels of Prdx6 in 6mo old female E4 carrier mice in absence of Aβ might impair their ability to reduce oxidized lipids and predispose them to membrane alteration. Moreover, aging and increase of Aβ load together might contribute to the reduction of GPx4 levels in APOE4 carriers and the accumulation of MBs.

Additional studies are required to clarify the underlying interaction sex-apoE allele in MBs onset and its contribution to the pathogenesis of AD.