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Amb el patrocini de:

P.35. SOLUBLE EPOXIDE HYDROLASE INHIBITORS COUNTERACT MICROGLIA PHENOTYPIC CHANGES INDUCED BY MONOMERIC C-REACTIVE PROTEIN: NEW PERSPECTIVES AGAINST NEUROINFLAMMATION IN ALZHEIMER'S DISEASE

Yuan Y[1], Bartra C[1], Valdés H[1], Martín-López J[2], Mullins JJ[3], Martínez N[2], Codony S[2], García-Lara E[1], Sawkulycz X[4], Morisseau C[5], Hammock BD[5], Vázquez S[2], Muñoz-Torrero D[2], Slevin M[4], Sanfeliu C[1]

[1] Institut d'Investigacions Biomèdiques de Barcelona (IIBB), CSIC and Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona.
[2] Facultat de Farmàcia i Ciències de l'Alimentació, and Institut de Biomedicina (IBUB), Universitat de Barcelona, Barcelona.
[3] Le Moyne College, Syracuse, NY.
[4] School of Life Sciences, Manchester Metropolitan University, Manchester.
[5] University of California Davis, Davis, CA.

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease worldwide. Neuroinflammation is a crucial neuropathological trait in AD, although the underlying mechanisms are not clarified. We previously proposed the monomeric C-reactive protein (mCRP), which is generated by activation and further disaggregation of blood CRP, as a trigger of AD neuropathology after cerebrovascular damage. mCRP is a potent pro-inflammatory agent found deposited in AD brain tissue and proved to induce AD-like dementia and tau and amyloid neuropathology in experimental models. Here we analysed the phenotypic changes induced by mCRP in microglia, the main effector cells of the inflammatory response. Then we tested the protective action of inhibiting the soluble epoxide hydrolase enzyme (sEH), a promising druggable target in AD. sEH inhibitors (sEHi) increase intracellular levels of anti-inflammatory epoxyeicosatrienoic acids (EETs). BV2 microglial cells were incubated with 50 or 100 µM mCRP for 24 h. Leading molecules of chemical families of newly synthesized sEHi (UB-JML-99 and UB-JM-39) were used for protective assays. mCRP activated the nitric oxide pathway as shown by increased release of nitric oxide and higher gene expression of iNOS, whereas sEHi agents blocked these effects. mCRP increased the release of TNFα into the media and the expression of pro-inflammatory cytokines and chemokines. Furthermore, mCRP modified the epigenetic microglial phenotype suggesting a dysregulated pattern. sEHi generally inhibited damaging effects of mCRP with a higher potency than the standard compound TPPU. Overall we demonstrated that mCRP directly activates microglia inflammatory pathways and may contribute to the triggering and progression of AD. Moreover, sEHi were confirmed as effective therapeutic molecules against neuroinflammation in an AD scenario.

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