Review of: "Targeting Alzheimer's disease hallmarks with the Nrf2 activator Isoeugenol"

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The endogenous antioxidant response pathway protects cells from oxidative stress by increasing the expression of cytoprotective enzymes and is regulated by the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2). In addition to regulating the expression of antioxidant genes, NRF2 has also been shown to exert anti-inflammatory effects and modulate both mitochondrial function and biogenesis. This is because mitochondrial dysfunction and neuroinflammation are features of many neurodegenerative diseases, and NRF2 has emerged as a promising therapeutic target. In this study, the potential of Isoeugenol, a skin allergen with electrophilic properties, to activate Nrf2 and revert some AD hallmarks, was investigated. This work was conducted in vitro (in mouse microglial cells exposed to LPS and neuronal cells overexpressing the human APP with the Swedish mutation, N2a-APPswe) and in vivo (in AD double transgenic mice, APP/PS1, intranasally administered with Isoeugenol), at an early (6-month-old animals) and late (11-month-old animals) AD stage. Overall, the results showed that Isoeugenol exhibits a good pharmacokinetic and pharmacodynamic profile. Isoeugenol activates Nrf2 and displays antioxidant and anti-inflammatory effects, and reduces the levels of Aβ peptides in in vitro and in vivo models of AD. In addition, its positive effect on metabolism was also demonstrated in vivo, as it reduced the triglyceride and LDL cholesterol levels in treated AD mice. Importantly, Isoeugenol improved the memory deficits observed in APP/PS1 mice, which was more evident in older animals (11-month-old), reinforcing its potential in ameliorating AD hallmarks, even at a late stage.

The work is highly appreciable. This research will show a promising pathway towards identifying another lead molecule for reverting the symptoms of AD through the activation of NRF2.