Is the modulation of reactive astrocytes a promising strategy for AD therapy? Preclinical experience with palmitoylethanolamide.

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Despite the great effort of preclinical research in the field of neurodegenerative diseases, and in particular for Alzheimer's disease, at present there are no efficacious therapies capable of inhibiting their onset or slowing their progression.
This evidence raises questions about the difficulty of transforming into effective interventions the interesting results deriving from numerous, and often, very promising preclinical data.
Such a difficulty might be due to the fact that preclinical research often begins with hypotheses arising from the theoretical paradigms of the disease rather than compelling evidence derived from the study of the patient. In this context, for many years researchers did not recognize, and accordingly investigated, the crucial role exerted by the astrocyte activation and neuroinflammation on the onset and progression of Alzheimer's disease. Today it is known that a marked glial activation triggers, among other things, the release of numerous cytokines and inflammatory mediators that amplify neuroinflammation, thereby contributing significantly to further neurodegeneration. Moreover, neuroinflammation contributes to neurogenesis inhibition. In this context, it is now demonstrated the crucial role exerted by astrocytes. They in fact undergo a significant morpho-functional transformation that, beside the ability to release pro-inflammatory molecules, at the same time makes them unable to fulfill their physiological supportive functions to neurons that, therefore, become more vulnerable to toxic substances released by the same glial cells in the environment. Therefore the modulation of these processes appears to be a promising strategy for therapeutic intervention. In this sense, the endogenous compound palmitoylethanolamide could represent a promising therapeutic agent for its demonstrated ability to inhibit neuroinflammatory processes responsible of neuronal death and neurogenesis inhibition. This assumption is further supported by recent evidence that palmitoylethanolamide is able to improve memory processes in rats administered with beta amyloid. All these findings, combined with the high safety profile of this compound, suggest an immediate translatability in humans based on the very encouraging and convincing results obtained from preclinical research.