Nitrones as Potential Neuroprotective Agents for the Treatment of Alzheimer's Disease

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Alzheimer's disease (AD) is a neurodegenerative disorder of high incidence worldwide for which there is currently no cure. Despite the causes of this disease are still controversial, it is known that amyloid plaques are a neuropathological feature associated with AD, which are related to the overproduction and deposition of β-amyloid peptide (Aβ) in brain tissue. According to the amyloid hypothesis, overproduction of Aβ is a consequence of the disruption of homeostatic processes regulating the proteolytic cleavage of the amyloid precursor protein (APP) proposing that Aβ deposition initiates a succession of events that finally lead to AD. Recently, it has been shown that caspase-3 is involved in the increase of Aβ by activation of GSAP (activating protein γ-secretase) responsible for generating Aβ41 and Aβ42 found in amyloid plaques. In the search of novel therapeutic agents against AD, in previous studies we have determined the ability of a group of nitrones (non-cytotoxic, free radical scavengers and capable of crossing the blood-brain barrier) to inhibit apoptosis and decrease active caspase-3 in a mouse hippocampal cell line (HT22). The main goal of this work was to evaluate the effect of these nitrones in APP processing and sub-cellular localization by Western blot assays and fluorescence microscopic analysis in order to find whether they are able to decrease Aβ peptide formation in cells. For this purpose, we used stable H4 human neuroglioma cells overexpressing APP attached to the fluorescent protein GFP. These cells have enhanced amyloidogenic processing by mutations in the DNA (cellular model clone AD). As control, HT22 and H4 wild-type cell lines expressing endogenous levels of APP were used. Interestingly, all the evaluated nitrones proved to be neuroprotective with some of them favouring the non-amyloidogenic processing pathway. Owing to its suitable pharmacological profile these molecules could become potential drugs for the treatment of AD.

Key words: processing of APP, caspase-3 inhibitors, nitrones.
Acknowledgments: ANII, PEDECIBA-QUÍMICA, CSIC