PQM130, A NOVEL FERULOYL-DONEPEZIL HYBRID COMPOUND, EXERTS NEUROPROTECTIVE EFFECTS AND AMELIORATES MEMORY IMPAIRMENTS IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

Fabiana Morroni[1], Giulia Sita[1], Agnese Graziosi[1], Letizia Pruccoli[2], Andrea Tarozzi[2], Patrizia Hrelia[1]
[1]Department of Pharmacy and BioTechnology - FaBiT, Alma Mater Studiorum, University of Bologna, Bologna - Italy, [2]Department for Life Quality Studies - QuVi, Alma Mater Studiorum - University of Bologna, Rimini - Italy

Introduction: Alzheimer's disease (AD) is the most common neurodegenerative disorder worldwide, characterized by memory loss, personality changes and cognitive dysfunction leading to dementia. Two hallmarks of neuropathology in AD are plaques, mainly composed of amyloid-beta (Aβ) peptide, and neurofibrillary tangles, formed by hyperphosphorylated tau. The events triggering AD pathology and the molecular mechanisms linking aging to AD are not known. The multifactorial nature of AD calls for the development of multitarget agents addressing key pathogenic processes. Donepezil, an acetylcholinesterase inhibitor, is a first-line acetylcholinesterase inhibitor used for the treatment of AD. Although extensive studies have demonstrated the symptomatic efficacy of donepezil treatment in patients with AD, the effects of donepezil, if any, on the AD process are not known. In the present study, a novel feruloyl-donepezil hybrid compound (PQM130) was synthesized and evaluated as multitarget drug candidate against the neurotoxicity of $A\beta_{1\text{-}42}$oligomers (AβO) in mice. PQM130 had already shown anti-inflammatory activity in the mice paw edema, pleurisy and formalin-induced hyperalgesy models, in vitro metal chelator activity for Cu^{2+} and Fe^{2+}, and neuroprotection of human neuronal cells against oxidative damage.

Methods: AβO was injected intracerebroventricularly in C57BL/6mice, and the treatment with PQM130 (0.5-1mg/kg) started 1hour after the surgery for the next 10 days. Subsequently, animals performed behavioral tests before the sacrifice.

Results: The intracerebroventricular (i.c.v.) injection of AβO into the mouse brain triggered increased reactive oxygen species levels, neurodegeneration, neuroinflammation, and memory impairment. In contrast, the intraperitoneal administration of PQM130 after i.c.v. AβO-injection counteracted oxidative stress and neuroinflammation, induced cell survival and protein synthesis through the modulation of key survival pathways. Additionally, PQM130 treatment decreased AβO-induced neuronal apoptosis, via caspase pathway. Moreover, PQM130 improved learning and memory, protecting mice against the decline in spatial cognition. Even more interesting is that PQM130 modulated different pathways compared to donepezil and it is much more effective in counteracting AβO damage.

Conclusions: Therefore, our findings highlighted that PQM130 is a potent multi-functional agent against AD and could act as promising neuroprotective compound for anti-AD drug development.

Supported by PRIN 2015(Prot. 20152HKF3Z)