OPEN ACCESS

Scientific Letters

II TOXRUN
International Congress 2023
27-28 April, 2023 | Porto, Portugal

Poster 21

Alzheimer's disease: the neuroprotective potential of novel synthetic compounds targeting P-glycoprotein

A. R. Monteiro [1,2,*], M. Maia [3,4], M. Martins [3,4], E. Sousa [3,4], F. Remião [1,2] and R. Silva [1,2]

[1] Associate Laboratory i4HB – Institute for Health and Bioeconomy, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira, 4050-313 Porto, Portugal
[2] UCIBIO – Applied Molecular Biosciences Unit, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira, 4050-313 Porto, Portugal
[3] Laboratory of Organic and Pharmaceutical Chemistry, Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal
[4] CIIMAR – Interdisciplinary Centre of Marine and Environmental Research, University of Porto, Novo Edificio do Terminal de Cruzeiros do Porto de Leixões, Avenida General Norton de Matos, S/N, 4450-208 Matosinhos, Portugal

* Correspondence: up202002446@edu.ff.up.pt

Abstract

Background: Alzheimer's disease (AD) is a progressive neurological disorder characterized by cognitive decline associated, specifically, with the degeneration of cholinergic neurons [1]. Although the etiology of the disease remains elusive, with several pathophysiological mechanisms contributing to disease progression, two main pathological hallmarks are well described, namely the presence of 1) neurofibrillary tangles formed by unfolded protein aggregates (hyperphosphorylation of tau protein) and 2) extracellular aggregates of Aβ within the brain [2, 3]. **Objective:** The present work aimed to perform a screening of the potential neuroprotective effects of 21 novel small molecules in a cholinergic-differentiation model of neuronal cells using the SH-SY5Y neuroblastoma cell line. **Methods:** SH-SY5Y cells were differentiated into a cholinergic phenotype in response to treatment of at least 7 days with retinoic acid at a final concentration of 10 μM, under low serum conditions [4, 5]. The assays selected to evaluate the potential neuroprotective effects were chosen to replicate some of the emerging disease-related hallmarks, namely: metal ion dyshomeostasis, ferroptosis and impairments in Aβ clearance [modulation of P-glycoprotein (P-gp) activity] [3, 6]. **Results:** The results of this study highlighted the remarkable neuroprotective effects of the majority of compounds against iron (III)- and erastin-induced cytotoxicity, in addition to their ability to modulate P-gp activity. Furthermore, the P-gp activators (compounds I-VIII, XII and XXI) were evaluated in a cellular model of AD-like pathology of Aβ-induced cytotoxicity. The obtained results demonstrated the ability of compounds to protect the differentiated cells against the toxic stimulus, implicating the ATP-dependent efflux pump - P-gp - in the clearance of Aβ aggregates. **Conclusions**: Thus, this study reinforces the several efforts that have been made toward counteracting AD multifactorial nature by shifting the strategy into the design of P-gp activators for preventing, delaying or treating AD.

Keywords: Alzheimer's disease; amyloid-beta; P-glycoprotein; neuroprotection; disease-modifying drugs

Acknowledgments

This research was funded by national funds from FCT - Fundação para a Ciência e a Tecnologia, I.P., in the scope of the projects UIDB/04423/2020, UIDP/04423/2020 (CIIMAR), UIDP/04378/2020 and UIDB/04378/2020 of the Research Unit on Applied Molecular Biosciences - UCIBIO and the project LA/P/0140/2020 of the Associate Laboratory Institute for Health and Bioeconomy - i4HB.

References

1. Hampel, H.; Mesulam, M.M.; Cuello, A.C.; *et al*. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain* **2018**, 141, 1917-1933.
2. Du, X.; Wang, X.; Geng, M. Alzheimer's disease hypothesis and related therapies. *Transl Neurodegener* **2018**, 7, 1-7.
3. Savelieff, M.G.; Nam, G.; Kang, J.; Lee, H.J.; Lee, M.; Lim, M.H. Development of multifunctional molecules as potential therapeutic candidates for Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis in the last decade. *Chem Rev* **2019**, 119, 1221-1322.
4. Zhang, Y.P.; Brown, R.E.; Zhang, P.C.; Zhao, Y.T.; Ju, X.H.; Song, C. DHA, EPA and their combination at various ratios differently modulated Aβ25-35-induced neurotoxicity in SH-SY5Y cells. *Prostaglandins Leukot Essent Fat Acids* **2018**, 136, 85-94.
5. Medeiros, L.M.; De Bastiani, M.A.; De Rico, E.P.; Schonhofen, P. Cholinergic differentiation of human neuroblastoma SH-SY5Y cell line and its potential use as an in vitro model for Alzheimer's disease studies. *Mol Neurobiol* **2019**, 56, 7355-7367.
6. Chai, A.B.; Hartz, A.M.S.; Gao, X.; Yang, A.; Callaghan, R.; Gelissen, I.C. New evidence for p-gp-mediated export of amyloid-β peptides in molecular, blood-brain barrier and neuronal models. *Int J Mol Sci* **2021**, 22, 1-20.