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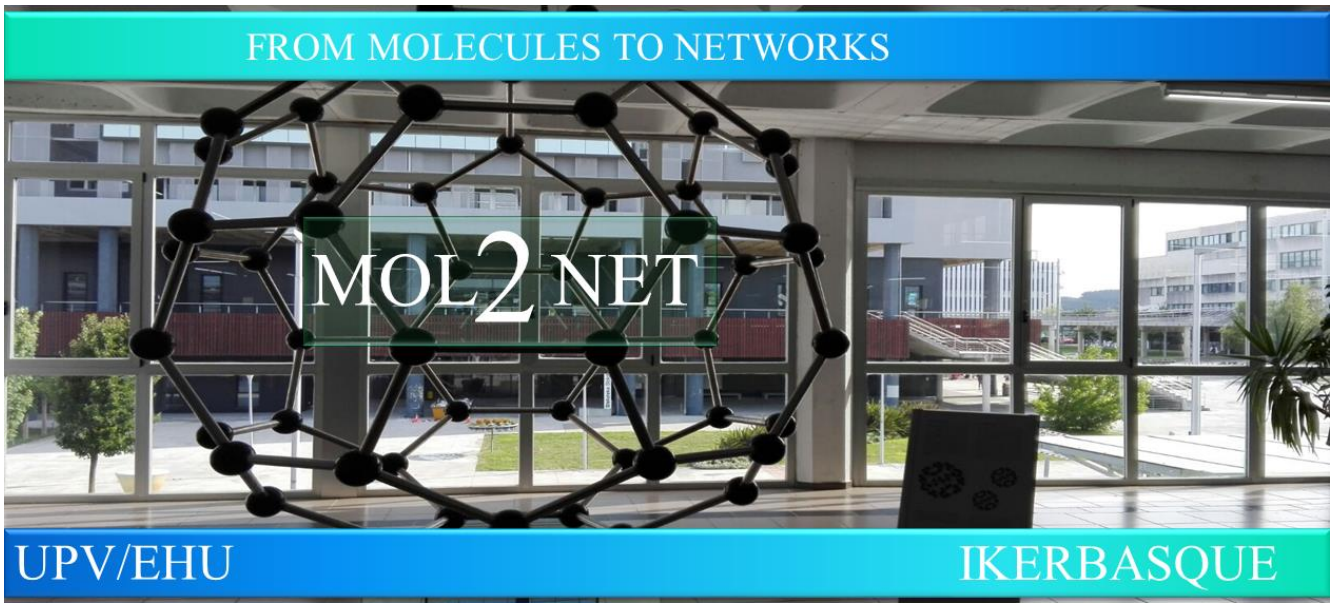

Retinoic acid isomers as promising molecules against Alzheimer's disease

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Graphical Abstract	Abstract.
	*Alzheimer's is a neurodegenerative and irreversible disease. In Alzheimer's disease, it is possible to identify the presence of insoluble amyloid β deposits in plaques in the brain. Retinoic acid isomers are being studied as a new alternative for Alzheimer's disease. In this work, the isomers are analyzed: all-trans retinoic acid, 9-cis retinoic acid and 13-cis retinoic acid. They may play an important role in AD by protecting neurons from β-amyloid-induced cell death.*

Introduction

Alzheimer's disease (AD) is defined as a neurodegenerative and irreversible disease, where individuals affected by AD have memory and cognitive impairment [1].

The brains of people with AD are characterized by loss of synapses, neuronal death, neurofibrillary tangles and amyloid plaques [2]. Neurofibrillary tangles are composed of hyperphosphorylated tau proteins, while amyloid plaques consist of amyloid β (Aβ) peptides [3].

AD is the most common form of dementia in the elderly, accounting for two-thirds of dementia cases in individuals aged 65 and over. It is estimated that the number of individuals with AD exceeds 15 million worldwide. With this, AD is considered a public health problem worldwide, so the search for treatments that can stop the disease becomes urgent [4,5].

Stereochemistry has played a key role in drug manufacturing and development[6]. Retinoic acid isomers: all-trans retinoic acid, 9-cis retinoic acid and 13-cis retinoic acid may play an important role in AD, protecting neurons from amyloid β-induced cell death [7].

Case Study

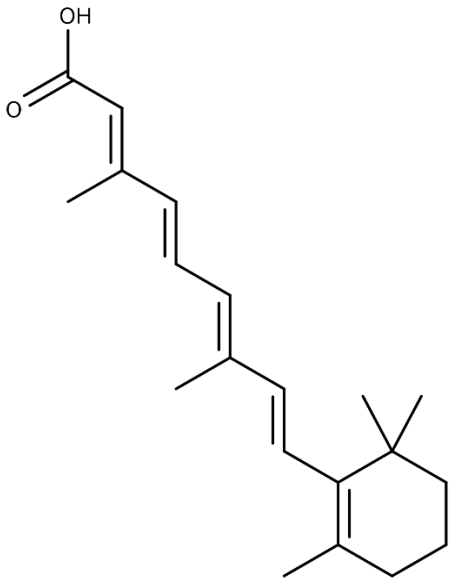
In the study by Sahin et al [7] they evaluated whether isomers of retinoic acid protect neurons from cell death induced by amyloid β. The verified isomers were: all-trans retinoic acid, 9-cis retinoic acid and 13-cis retinoic acid (Figure 1). For this, a procedure was performed where the neurons of mice

cultured for 8 days were exposed to amyloid β for 24 hours, and the apoptodic cells were determined through morphological criteria and Hoechst 33258 labeling. Neurons that were in control medium for 24 hours had 16% apoptotic nuclei, while amyloid β increased the amount of apoptotic neurons from a 16% percentage in controls to 81%.

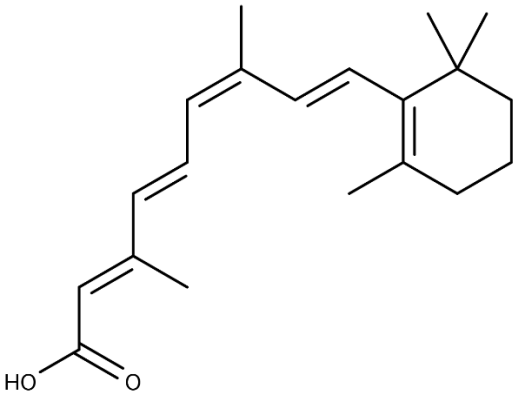
As a result, all-trans retinoic acid, 9-cis retinoic acid and 13-cis retinoic acid at concentrations of 0.01 μM, 0.1 μM and 1 μM were able to reduce the percentage of apoptotic neurons. It was found that the 1 μM isomer had a better efficacy than the 0.1 μM isomer, as well as the 0.1 μM isomer was more effective than the 0.01 μM isomer. Cells treated with retinoic acid together with amyloid β may proliferate and possibly a reduction in the proportion of apoptodic cells.

In Alzheimer's disease, it is possible to identify deposits of insoluble amyloid β in plaques in the brain. Consequently, insoluble β amyloid can induce the death of apoptotic neuronal cells. The retinoic acid isomers: all-trans retinoic acid, 9-cis retinoic acid and 13-cis retinoic acid have an anti-apoptotic effect against amyloid β.

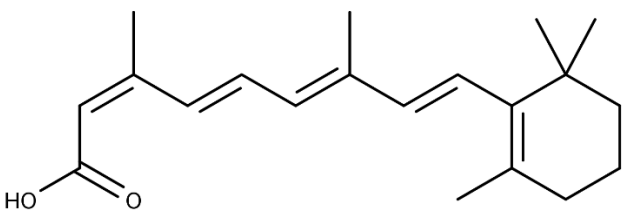
Figure 1. Chemical structures of compounds: all-trans retinoic acid, 9-cis retinoic acid and 13-cis retinoic acid



All-trans retinoic acid



9-cis retinoic acid



13-cis retinoic acid

Eftekhari et al [8] developed a study where it was reported that the term retinoid corresponds to molecules that depend on vitamin A, these include retinol and its biological precursors, carotenoids and retinoic acid that activates gamma, beta and alpha receptors.

Vitamin A is considered fat-soluble, and can be of animal origin, which is in the form of retinol or fatty acid ester, and of plant origin, which is β-carotene. Retinoid and β-carotene molecules have antioxidant properties.

All-trans retinoic acid is one of the constituents of the retinoid group, and is metabolized into 9-cis retinoids and 13-cis-retinoids. The active form of retinoids is retinoic acid, which couples and activates alpha, beta, and gamma retinoic acid receptors. 13-cis retinoic acid also forms retinoid, but in a smaller amount than retinoic acid. The authors report that 9-cis retinoic acid is a retinoic acid compound and interacts with alpha, beta and gamma retinoic acid receptors, activating them. During the study, retinoic acid regulated gene expression at retinoic acid receptors, and antioxidant properties were also observed.

Retinoic acid isomers were also addressed by Lee and Contributors[9]. The authors observed that the all-trans retinoic acid and 13-cis retinoic acid isomeres are more stable than 9-cis retinoic acid. Furthermore, 13-cis retinoic acid has better pharmacokinetic properties than 9-cis retinoic acid, having a longer half-life.

Therefore, it was observed that 13-cis retinoic acid failed to deliver a clinical benefit in individuals with neuroblastoma. The 13-cis retinoic acid demonstrates little efficiency of penetration in the brain cells of the all-trans retinoic acid, because the all-trans retinoic acid is a lipophilic molecule and because of that, it can be diffused more easily in the cell membrane, unlike of 13-cis retinoic acid.

It was also emphasized by the authors that retinoic acid as a signaling molecule is recommended that all-trans retinoic acid is the best biologically active form. In the study, it was possible to observe that retinoic acid seems to act in pathways and mechanisms that are recurrent in Alzheimer's disease.

In the study by Zhao et al [10] the authors reported that retinoic acid isomers play an important role in cell differentiation, proliferation and apoptosis. Retinoic acid isomers also play a role in the central nervous system in regulating neuronal patterning, axonal growth, differentiation, neuronal plasticity, and nerve regeneration. In addition, retinoic acid isomers can act as immunomodulators, essential for the maintenance of the immune system.

The authors report that the all-trans retinoic acid isomer may be a protector against oxidative damage and apoptosis in neurons. While the 9-cis retinoic acid isomer has protective effects on neurons shortly after stroke by increasing the release of growth factors.

In the study it is reported that people who have Alzheimer's disease have a lower concentration of vitamin A, C, E and β-carotene. Therefore, the authors found studies that indicated the involvement of isomers with vitamins A and retinoic acid in Alzheimer's disease.

One of the main causes of Alzheimer's disease is the deposition and accumulation of amyloid peptides, cleaved from the amyloid precursor protein in the brain. In contrast, the all-trans retinoic acid isomer can inhibit the course of the amyloid precursor protein. Furthermore, the 9-cis retinoic acid isomer suppresses amyloid β synthesis in vitro. With this, it is possible that retinoic acid isomers deliver positive effects for the treatment of Alzheimer's disease.

Conclusions

Based on the results of the studies, it is concluded that the isomers all-trans retinoic acid, 9-cis retinoic acid and 13-cis retinoic acid have beneficial effects for Alzheimer's disease. Specifically, the all-trans retinoic acid isomer behaved more stable than 9-cis retinoic acid, and more efficiently penetrated brain cells than 13-cis retinoic acid. However, retinoic acid isomers have developed an important role in cognitive activities and anti-amyloidogenic properties. Thus, retinoic acid isomers are a suggestion for new therapies for Alzheimer's disease.

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