MODELING OF IBUPROFEN CONJUGATES WITH ENALAPRILAT AND ARGATROBAN AND THEIR COMPLEXES WITH MONOMERIC AND PROTOFIBRILLAR FORMS OF B-AMYLOID PEPTIDE

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Alzheimer's disease (AD) is a form of dementia characterized by the accumulation of β-amyloid peptide (Aβ) in the central nervous system. Ibuprofen (IBU), a nonsteroidal anti-inflammatory drug, can facilitate the clearance of Aβ from the central nervous system by, according to our data, enhancing the interaction of Aβ with its main depot, human serum albumin (HSA), and by inhibiting the formation of Aβ fibrils. Conjugates of IBU with drugs have demonstrated neuroprotective, anti-inflammatory, antioxidant, and anticholinesterase properties in vitro experiments and in animal models of AD. According to our data, enalaprilat ENA (angiotensin-converting enzyme inhibitor) and argatroban ARG (anticoagulant, thrombin inhibitor) exhibit properties similar to IBU in enhancing the inhibitory activity of HSA on Aβ fibril formation. To develop anti-AD agents with a comprehensive effect on Aβ metabolism, we modeled the structures of IBU-ENA and IBU-ARG conjugates using ChemDraw software, followed by energy minimization in the MM2 force field. The resulting structures were used to model their complexes with the monomeric and protofibrillar forms of Aβ40 using AutoDock Vina, with calculation of the energy characteristics of the studied interactions and the corresponding equilibrium dissociation constants of the complexes, Kd. It was predicted that conjugation of ENA and ARG with IBU decreases the Kd value for the interaction of IBU with the Aβ monomer by 5.5 and 35 times, respectively, and for the interaction of IBU with the protofibrillar form of Aβ, the Kd values of the ENA and ARG conjugates are reduced by 2 and 56 times, respectively. An analysis of contact residues allowed us to predict the amino acid residues of the binding sites of the studied conjugates with the monomeric and protofibrillar forms of Aβ40. The IBU conjugates with ENA and ARG are subject to further experimental confirmation of their ability to influence the HSA-Aβ equilibrium and Aβ fibril formation, preventing Aβ deposition and AD progression. This work was supported by grant No. 25-24-01143 from the Russian Science Foundation (M.P. Shevelyova).