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The low-molecular-weight ligands of human serum albumin, promoting its interaction with amyloid β peptide

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One of the functions of human serum albumin (HSA) in blood and cerebrospinal fluid is a sequestration of amyloid β peptide (Aβ), the important participant of Alzheimer's disease (AD) progression. The therapeutically advantageous enhancement of Aβ trapping can be achieved via directed improvement of HSA affinity to Aβ. Previously, we demonstrated that arachidonic/linoleic acids (ArA/LA) favor Aβ binding to HSA. In this study, we explored a panel of the low-molecular-weight HSA ligands associated with AD (ibuprofen (IBU), serotonin (SRO) and tryptophan (TRP)) with regard to their ability to affect the HSA-Aβ interaction. Molecular modelling predicts an overlap between the HSA-binding sites of IBU and ArA in the region of fatty acid binding site 3 (FA3). Similarly, the intersection between the Aβ-binding sites of HSA and its sites for ArA (FA6), SRO, TRP, IBU binding suggests their influence on HSA-Aβ interaction. The equilibrium and kinetic parameters of HSA interaction with monomeric Aβ40/42 in the presence/absence of the ligands was studied by surface plasmon resonance spectroscopy. The therapeutic IBU level decreases the equilibrium dissociation constant for the HSA-Aβ40/42 complexes by a factor of 3-5. SRO increases HSA affinity to Aβ40/42 by a factor of 7/17, whereas the structurally homologous TRP is inactive in this sense. Overall, we have shown high potency of the low-molecular-weight ligands to promote HSA interaction with Aβ, and laid the foundation for rational search of the substances with therapeutic potential in the treatment of AD.
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