In silico evidence of direct interaction between statins and ?-amyloid

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Introduction: Aggregation of amyloid-? (A?) peptides represents a crucial step in the pathogenesis of Alzheimer disease (AD). Compelling evidence from preclinical studies has established that statins may reduce amyloidogenesis and A?-mediated neurodegeneration, supporting a potential role of statin treatment in the prevention of AD. Different statins have been shown to interfere indirectly with A? production and clearance through either cholesterol-dependent or cholesterol-independent mechanisms. However, whether there may be a direct interaction between statins and A? metabolism is still unclear. Materials and methods: To test the possible direct interaction between statins and A?, we performed an in silico study by testing the orientation of different ligands, including statins and sulindac (the standard ligand of A?), in the A? active site using molecular operating environment (MOE) software. Results: Docking experiments showed that all the tested statins could directly interact with A? protofibrils. Among statins, pitavastatin had the strongest interaction with A? (pk i = 7.66), followed by atorvastatin (pk i = 7.63), rosuvastatin (pk i = 6.99), fluvastatin (pk i = 6.96), pravastatin (pk i = 6.46), lovastatin (pk i = 6.37), and simvastatin (pk i = 5.90). According to the above-mentioned results, pitavastatin, atorvastatin, rosuvastatin, and fluvastatin had a stronger binding to A? compared with the standard ligand sulindac (pk i = 6.62). Conclusion: This study showed a direct interaction between statins and A? protofibrils, which may underlie the protective role of this widely used class of drugs against amyloidogenesis and A?-mediated neurodegeneration. © 2018 Wiley Periodicals, Inc.

Alzheimer's disease (AD)

amyloid-? (A?)

docking

statins

amyloid beta protein

atorvastatin

fluindostatin

hydroxymethylglutaryl coenzyme A reductase inhibitor

mevinolin

pitavastatin

pravastatin

rosuvastatin

simvastatin

sulindac

amyloid beta protein

hydroxymethylglutaryl coenzyme A reductase inhibitor

Article

computer model

controlled study

crystal structure

drug protein binding

enzyme active site

molecular docking

molecular operating environment software

priority journal

protein metabolism

software

Alzheimer disease

chemistry

human

metabolism

molecular docking

pathology

Alzheimer Disease

Amyloid beta-Peptides

Catalytic Domain

Humans

Hydroxymethylglutaryl-CoA Reductase Inhibitors

Molecular Docking Simulation