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MEETING ABSTRACTS

DUAL BINDING SITE INHIBITORS OF ACETYLCHOLINESTERASE AS THERAPEUTIC TREATMENTS FOR ALZHEIMER'S DISEASE: ANY NEED FOR AN UPDATE?

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Alzheimer's disease (AD) is a broadly spread neurodegenerative disorder of ageing population manifesting itself in progressing loss of cognitive functions down to total demolition of intellect and disability. Profound synaptic dysfunction contributes to early loss of short-term memory in Alzheimer's disease. Here we show the protective effects against amyloid-induced synaptic toxicity of C-35, a potent reversible inhibitor of acetylcholinesterase (AChE).

Crystal structure of the complex between human AChE and C-35 revealed tight contacts of ligand along the enzyme active site gorge. Molecular dynamics simulations indicated that the external flexible part of the ligand establishes multiple transient interactions with the enzyme peripheral anionic site. Thus, C-35 is a dual binding site inhibitor of AChE.

In amyloid-transgenic mice, C-35, when administered after disease onset, reversed synapse loss, decreased the number of amyloid plaques and restored learning and memory. When administration of C-35 and the clinically relevant AChE dual inhibitor donepezil was terminated three weeks after the trial started, animals, that were receiving C-35 showed a much better ability to learn than those who received physiological saline or donepezil. Our results provide evidence that C-35 has a more pronounced Alzheimer's disease-modifying action than donepezil.

Keywords: Alzheimer's disease; inhibitors of cholinesterase; methyluracil derivatives; β-amyloid

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