

ORAL PRESENTATIONS

MOLECULAR TARGETS OF CNEURO-201: EVIDENCE FROM BIOPHYSICAL, CELLULAR, AND PRECLINICAL ANIMAL STUDIES

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Several neurodegenerative diseases, including Alzheimer’s disease (AD) and Tauopathies, are characterized by pathological protein aggregation – a key hallmark of proteinopathies. The novel class of synthetic naphthalene derivatives CNEURO-201 exhibits a multifaceted activity profile against key molecular targets associated with AD.

Among promising therapeutic agents, the class of naphthalene derivatives CNEURO-201 stands out. The goal of our study was to characterize the pharmacological properties and elucidate the molecular mechanisms of action of these compounds. Amylovis 1 demonstrated the lowest cytotoxicity (IC₅₀ = 9,1 mM) compared to Amylovis 2 (3,1 mM) and Amylovis 3 (1,4 mM). In the cellular model of proteinopathy, Amylovis 1 showed the highest activity in suppressing protein aggregation. The results of molecular modeling and isothermal titration calorimetry showed that Amylovis 1 binds stably to the A β ₁₋₄₂ peptide (K_D = 0,68 μ M). The key interaction sites are located in regions 17–22 and 35–40 of the peptide and include residues Phe19 and Phe20. The binding is entropically driven.

Notably, CNEURO-201 and its related derivatives showed only marginal inhibition of acetylcholinesterase and butyrylcholinesterase ($\leq$ 4.5% at 20 μ M) and displayed low radical-scavenging activity in the ABTS assay.

Chronic administration of CNEURO-201 to 5xFAD model mice of AD failed to reverse the phenotypic behavioral changes, however significantly decreased amyloid burden in frontal cortex and hippocampus. The comprehensive analysis confirms that Amylovis 1 is a promising neuroprotective agent with a targeted mechanism of action aimed at suppressing A β aggregation.

CNEURO-201 does not prevent the onset of motor dysfunction in Tau-P301S mice but significantly slows its progression during the first two weeks after symptom manifestation and preserves grip strength throughout the symptomatic phase. The compound extends median survival by 7 days without reducing overall mortality.

The favorable cytotoxicity profile and the ability to modulate protein aggregation in cellular models justify further development of the compound as a potential therapeutic agent for Alzheimer’s disease and related proteinopathies.

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