Tipo	Periódico
Título	Design, in silico and pharmacological evaluation of a peptide inhibitor of BACE-1
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Programa/Curso (s)	Programa de Pós-Graduação Stricto Sensu em Ciências da Saúde
DOI	10.3389/fphar.2023.1184006
Assunto (palavras chaves)	BACE-1; competitive inhibitor; in silico design; peptide; pharmacokinetics.
Idioma	Inglês
Fonte	Título do periódico: Front Pharmacol ISSN: 1663-9812 Volume/Número/Paginação/Ano: 14:1184006, 2023.
Data da publicação	16/06/23
Formato da produção	Impressa ou digital
Resumo	Introduction: Alzheimer's disease (AD) is the main type of dementia, caused by the accumulation of amyloid plaques, formed by amyloid peptides after being processed from amyloid precursor protein (APP) by γ- and ß-secretases (BACE-1). Although amyloid peptides have been well established for AD, they have been found in other neurodegenerative diseases, such as Parkinson's disease, Lewy body dementia, and amyotrophic lateral sclerosis. Inhibitors of BACE-1 have been searched and developed, but clinical trials failed due to lack of efficacy or toxicity. Nevertheless, it is still considered a good therapeutic target, as it was proven to remove amyloid peptides and improve memory. Methods: In this work, we designed a peptide based on a sequence obtained from the marine fish Merluccius productus and evaluated it by molecular docking to verify its binding to BACE-1, which was tested experimentally by enzymatic kinetics and cell culture assays. The peptide was injected in healthy mice to study its pharmacokinetics and toxicity. Results: We could obtain a new sequence in which the first N-terminal amino acids and the last one bound to the catalytic site of BACE-1 and showed high stability and hydrophobicity. The synthetic peptide showed a competitive inhibition of BACE-1 and Ki = 94 nM, and when injected in differentiated neurons, it could reduce Aβ42o production. In plasma, its half-life is ∼1 h, clearance is 0.0015 µg/L/h, and Vss is 0.0015 µg/L/h. The peptide was found in the spleen and liver 30 min after injection and reduced its level after that, when it was quantified in the kidneys, indicating its fast distribution and urinary excretion. Interestingly, the peptide was found in the brain 2 h after its administration. Histological analysis showed no morphological alteration in any organ, as well as the absence of inflammatory cells, indicating a lack of toxicity. Discussion: We obtained a new BACE-1 inhibitor peptide with fast distribution to the tissues, without accumulation in any organ, but found in the brain, with the possibility to reach its molecular target, BACE-1, contributing to the reduction in the amyloid peptide, which causes amyloid-linked neurodegenerative diseases.
Fomento	FAPESP