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DEVELOPMENT OF THE PEPTIDE HUMAN INSULIN-DEGRADING ENZYME INHIBITOR JURA AND ANALYSIS OF ITS INHIBITORY ACTIVITY *

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Abstract

Based on molecular dynamics modeling, a novel peptide human insulin-degrading enzyme (IDE) inhibitor **Jura** is proposed. Its primary structure matches with IDE sequence region. It has been demonstrated that **Jura** peptide has the activity to inhibit IDE through a competitive mechanism with an inhibition constant of about 10 nM. The possibility of using the **Jura** peptide for the treatment of type II diabetes and a number of neurodegenerative diseases is being discussed.

Insulin-degrading enzyme (IDE, EC 3.4.24.56) — a secreted protein with the specific proteolytic activity of insulin, other protein and peptide substrates (beta-amyloid peptide, glucagon, amylin and calcitonin) [1]. Its ability to cleave polypeptides in amyloid-like fibrils is associated with the molecular mechanisms of the development of Alzheimer's disease [2] and type II diabetes [3]. Peptide IDE inhibitors can potentially be used in the treatment of type II diabetes [4] and a number of neurodegenerative diseases [5].

Based on the results of the molecular dynamics modeling of the enzyme structure evolution, a potentially inhibitory peptide **Jura** was proposed, which sequence matches with IDE 995-1009 amino acids residues. The inhibitory activity of **Jura** against the reaction of IDE with a fluorogenic substrate was assessed. A decrease in the rate of hydrolysis of the fluorogenic substrate IDE was observed *in vitro* in the presence of **Jura**. In order to determine the mechanism of **Jura** + IDE interaction, kinetic graphs were plotted in Dixon coordinates 1/V([I]). It has been shown that **Jura** is an effective competitive inhibitor of IDE, with an inhibition constant K_I = 50 nM. The products of the enzymatic reaction **Jura** + IDE and insulin + IDE, as well as dissolved **Jura**, were analyzed by mass spectrometry method. It has been observed that **Jura** undergoes proteolysis at three positions after interaction with IDE.

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