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Biochimica et Biophysica Acta 1758 (2006) 320 – 327
BIOCHIMICA ET BIOPHYSICA ACTA
BBA
http://www.elsevier.com/locate/bba

Review

Rational design of complementary peptides to the βAmyloid 29–42 fusion peptide: An application of PepDesign

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Received 18 August 2005; received in revised form 5 October 2005; accepted 6 October 2005
Available online 25 October 2005

Abstract

Peptides in solution currently exist under several conformations; an equilibrium which varies with solvent polarity. Despite or because of this structure versatility, peptides can be selective biological tools: they can adapt to a target, vary conformation with solvents and so on. These capacities are crucial for cargo carriers. One promising way of using peptides in biotechnologies is to decipher their medium–sequence–structure–function relationships and one approach is molecular modelling. Only few "in silico" methods of peptide design are described in the literature. Most are used in support of experimental screening of peptide libraries. However, the way they are made does not teach us much for future researches. In this paper, we describe an "in silico" method (PepDesign) which starts by analysing the native interaction of a peptide with a target molecule in order to define which points are important. From there, a modelling protocol for the design of 'better' peptides is set. The PepDesign procedure calculates new peptides fulfilling the hypothesis, tests the conformational space of these peptides in interaction with the target by angular dynamics and goes up to the selection of the best peptide based on the analysis of complex structure properties. Experimental biological assays are finally used to test the selected peptides, hence to validate the approach. Applications of PepDesign are wide because the procedure will remain similar irrespective of the target which can be a protein, a drug or a nucleic acid. In this paper, we describe the design of peptides which binds to the fusogenic helical form of the C-terminal domain of the Aβ peptide (Aβ29–42).

Keywords: Alzheimer; Amyloid; Angular dynamic; ApoE; Complementary peptide; Computer-aided design; In silico design; Peptide interaction; Tilted peptide

Contents

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doi:10.1016/j.bbamem.2005.10.001

1. Introduction

Despite the promising future of peptides in drug discovery, few methods of rational design of peptides are described in the literature. Several groups made peptides which inhibit a target protein with high affinity. They used peptide libraries expressed in phages or synthesized by solid-phase. Notably, Kasher et al. [1] and Katchalski et al. [2] designed peptides with a high affinity for α-Bungarotoxin (α-BTX), a toxic snake neurotoxin; these peptides inhibit the α-BTX binding to acetylcholine receptor (AchR) at the neuromuscular junction. They proposed a general approach named "systematic residue replacement" (SRR): they screened peptide libraries to identify a lead, characterized its interaction with the target by NMR or X-ray and performed a restricted SRR of the lead using residues categorized into 6 groups according to their physico-chemical properties. This method gave very good results but requires numerous biological assays in order to select the best peptides.

Other groups used molecular dynamics in order to simulate the interaction of a peptide with a target. Yang et al. [3] designed a peptide which had potential bioactivity to antagonize the function of human interleukin-6 (hIL-6) using molecular modelling and molecular dynamics trajectory analysis. However, due to the time required for molecular dynamics calculation, this method allows to test only few peptides.

We developed an "in silico" method named "PepDesign" to propose peptides with selected binding patterns. In this paper we used the method to make a binding partner to the helical form of Aβ29–42 peptide. By analogy to the SSR method, new peptides are designed by residue substitution of a template. The procedure is automatic up to the selection of molecules with improved interaction with the target. Experimental assays come as the validation and quantification of the peptide quality.

Aβ29–42 is implicated in the formation of senile plaques of Alzheimer's disease [4–6]. The peptide is known to have several conformations, from random coil to helix and to beta-extended forms. Because of its high hydrophobicity, the latter is responsible for the peptide aggregation often observed in NMR experiments. Beta aggregates are considered as a denaturated stable structural conformation. Before the peptide is aggregating, a transient helical form might have peculiar biological properties because of its hydrophobicity profile [7]. It should be a tilted peptide like the helical conformations of the N-terminal fragments of fusion proteins of several viruses such as SIV (Simian Immunodeficiency Virus) [8] or BLV (Bovine Leukaemia Virus) [9]. Tilted peptides are short fragments (10–20 residues) with an asymmetric hydrophobicity gradient along their helix axis. Their mean hydrophobicity leads them to insert into membranes and the assymmetric profile of this hydrophobicity allows them to insert tilted with an angle ranging from 30° to 60° with respect to the membrane surface. The tilted orientation is thought to destabilize membranes and to induce processes such as fusion [7]. The Aβ29–42 peptide induces liposome fusion in relation with its helix hydrophobicity properties [10].

A relationship exists between the type of ApoE (ε_2, ε_3 and ε_4) allele in human and the risks to develop the Alzheimer's disease. For a while, the debate was whether the ε_2 and ε_3 allele of ApoE prevented from, or whether the ε_4 allele was a risk factor for the Alzheimer's disease. We supported that the ε_2 and ε_3 alleles prevent the disease because we found that their C-terminal parts interact specifically with the C-terminal domain of the amyloid peptide. Interestingly, this interaction partially inhibited Aβ29–42 fusogenic properties on liposomes in vitro [11]. In contrast, the ε_4 allele of apolipoprotein E as well as fragments of apolipoprotein A1 failed to inhibit the amyloid peptide fusogenic properties supporting the specificity of the ε_2 and ε_3 apolipoprotein effects [11–13]. It was then demonstrated that the 200–299 fragment of ApoE can have a direct interaction with the C-part of Aβ in vitro [11]. Parallely, Lins et al. [14] studied the ApoE–Aβ interaction by molecular modelling and suggested that the minimal binding site of apolipoprotein E was in its helix 270–287.

Using the "in silico" PepDesign method, we attempted the rational design of complement peptides to Aβ29–42 by taking the ApoE270–287 fragment as a lead and looking for an improved stability of its interaction with Aβ. First, we reproduced the complex described by Lins et al. [14] and identified the key-residues of interaction. Mutant peptides were then generated by residue substitution. Energies of interaction of mutants with Aβ29–42 were computed. We selected peptides likely to show a stronger interaction with Aβ29–42 than the native apolipoprotein peptide and analysed the reasons for the improvement. Mainly two classes of mutants were