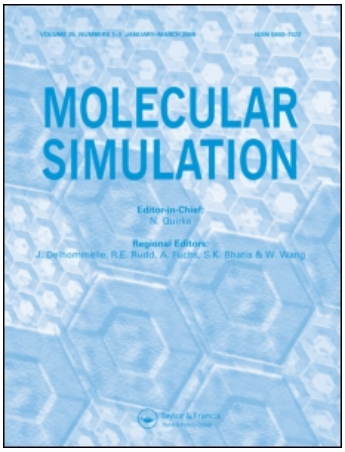

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Simulation of the Lipophilic and Antigenic Cores of the Aβ(1-42) Peptide of Alzheimer's Disease

Peter P. Mager[a]; Katrin Fischer[a]
[a] Research Group of Pharmacochemistry, Institute of Pharmacology and Toxicology of the University, Leipzig, Saxony, Germany

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SIMULATION OF THE LIPOPHILIC AND ANTIGENIC CORES OF THE Aβ(1–42) PEPTIDE OF ALZHEIMER'S DISEASE

PETER P. MAGER* and KATRIN FISCHER

Research Group of Pharmacochemistry, Institute of Pharmacology and Toxicology of the University, D-04107 Leipzig, Härtelstr. 16-18, Saxony, Germany

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The monomeric Aβ(1–42) peptide of Alzheimer's disease was studied. The peptide is an intrinsically soluble peptide; the N-terminal amino acids are more hydrophilic than the amino acids at the C-terminus. A first hydrophobic core was found at the middle area of the residues (GlN15 to Phe19), a second core at the end (Lys28 to Ala41). There is an antigenic potential at the begin of the sequences and the middle region of the Aβ(1–42) peptide. It is suggested that the middle area has an "amyloidogenic potential" by forming noncovalent interactions between paired, antiparallel β-sheet conformations. A perspective in drug research is to develop compounds that inhibit the associations between monomeric β-strains.

Keywords: Aβ(1–42) peptide; Alzheimer's disease; Lipophilic cores

1. INTRODUCTION

Alzheimer's disease (AD) is a chronic, neurodegenerative disorder which is characterized by pathological brain lesions composed of amyloid deposition [2, 3, 6–10]. The major protein constituent of the deposits is the so-called amyloid β-peptide (Aβ). It was demonstrated that freshly prepared random-coil conformation of Aβ(1–40) and Aβ(1–42) are nontoxic or less toxic, while an enhanced neurotoxicity is observed after inducing an aging of a β-sheet conformation by a suitable chemical solution conditions [1, 5, 8].

*Corresponding author. e-mail: magp@server3.medizin.uni-leipzig.de

This protein-conformation dependent disorder that is both genetically and risk-factor based, is believed to be a crucial (but not absolute) determinant in the pathogenesis of Alzheimer's disease.

TABLE I Sequence of the Aβ(1–43) molecule. The NH_2 and COOH terminal moieties are in 1 and 43 position, respectively. If the studied Aβ(1–42) peptide is considered, the N- and C-terminal moieties are in positions 1 and 42, respectively

Position	*Acid*
1	Asp
2	Ala
3	Glu
4	Phe
5	Arg
6	His
7	Asp
8	Ser
9	Gly
10	Tyr
11	Glu
12	Val
13	His
14	His
15	GlN
16	Lys
17	Leu
18	Val
19	Phe
20	Phe
21	Ala
22	Glu
23	Asp
24	Val
25	Gly
26	Ser
27	Trp
28	Lys
29	Gly
30	Ala
31	Ile
32	Ile
33	Gly
34	Leu
35	Met
36	Val
37	Gly
38	Gly
39	Val
40	Val
41	Ile
42	Ala
43	Thr

It was hypothesized by molecular simulation that the driving force of amyloid formation is based on noncovalent, hydrophobic interactions between monomeric pairs of antiparallel β-sheets of the Aβ peptides [5]. The aim of this study is to investigate whether there are lipophilic clusters of amino acids of the Aβ(1–42) peptide.

2. METHOD

The hydrophobicity index was determined according to Kyte and Doolite [4]. The antigenicity was predicted according Welling *et al.* [11].

3. RESULTS AND DISCUSSION

The primary structure of the Aβ(1–43) peptide is given in Table I. First, the peptide was categorized in various segments [1, 6, 10], and the distribution coefficients P (expressed as log$P$) were determined in dependence of the pH values (Tab. II). It can be seen that (i) the monomeric, purified Aβ peptides are soluble in water, (ii) the degree of solubility depends on the pH, (iii) the C-terminal amino acids are less hydrophilic than the amino acids at the N-terminus, and (iv) the hydrophilicity of the N-terminus depends more strongly on the pH of the tissues than the hydrophilicity of the C-terminus.

The plot of the hydrophobicity index against the sequence of amino acids (Fig. 1) shows that two peptide areas exist which have important physicochemical properties. The first core is found at the middle area of the residues (GlN15 to Phe19), the second core at the end (Lys28 to Ala41). It is hypothesized that the driving forces of amyloid formation are based on interactions between hydrophobic cores of monomeric, antiparallel β-sheets. It should be mentioned that a maximum aggregation of Aβ peptides to

TABLE II Distribution coefficients P (octanol/water, expressed as log$P$ values) synthetic Aβ(1–14) to Aβ(30–43) peptides that represent distinct region the Aβ peptide

	pH values							
Peptide	1.0	2.0	5.0	6.0	6.6	7.0	7.4	8.0
1–14	−18.72	−18.61	−13.62	−12.89	−12.89	−13.30	−13.46	−14.0
15–29	−12.85	−12.25	−9.14	−8.23	−7.69	−7.33	−7.08	−6.9
30–39	−3.72	−3.68	−3.42	−2.70	−3.03	−2.38	−2.36	−1.9
30–40	−2.64	−2.64	−2.62	−2.50	−2.25	−1.99	−1.68	−1.2
30–43	−1.96	−1.45	−1.33	−1.33	−1.34	−1.35	−1.39	−1.5

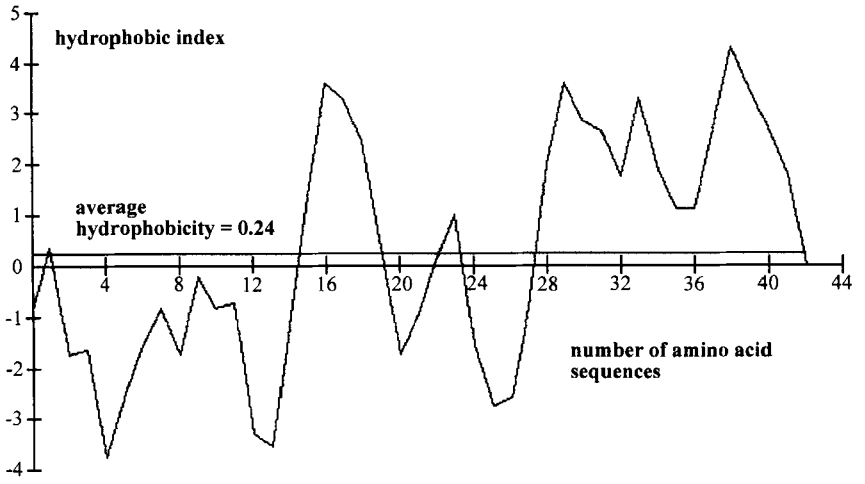

FIGURE 1 Hydrophobicity index plotted against the sequence of amino acids of Aβ(1–42).

unsoluble amyloids occurred at *p*H 6, which near the isoelectric point (IP = 5.5) of the Aβ(1–42) peptide, which also suggests that a net zero charge of the peptide favors aggregation, that is, noncovalent interactions play a dominant role.

Considering the predicted antigenicity profiles (Fig. 2), one may hypothesize that there is a strong "antigenic potential" at the begin of the sequences and the middle region of the Aβ(1–42) peptide.

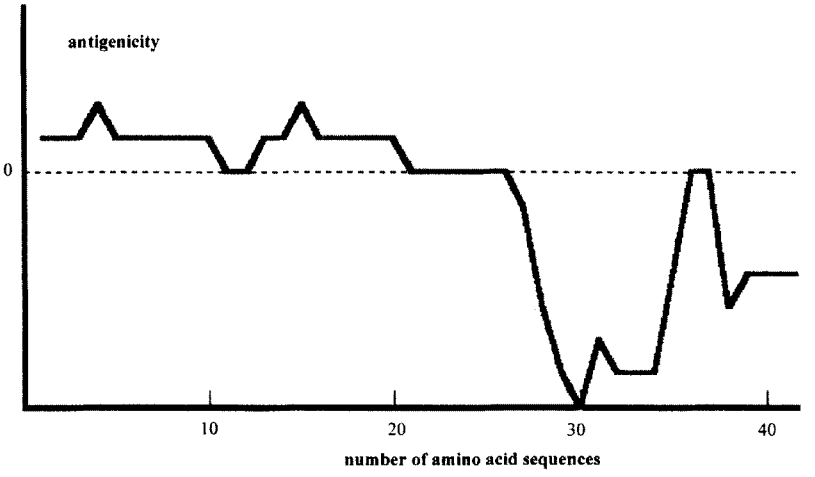

FIGURE 2 Antigenicity potential.

4. CONCLUSIONS AND FUTURE PERSPECTIVE

The Aβ(1–42) peptide of Alzheimer's disease was studied. The monomeric, purified Aβ peptides are soluble in water. Their degree of solubility depends on the *p*H. The C-terminal amino acids are less hydrophilic than the amino acids at the N-terminus, and the hydrophilicity of the N-terminus depends more strongly on the *p*H of the tissues than the hydrophilicity of the C-terminus. A first hydrophobic core was found at the middle area of the residues (GlN15 to Phe19), a second core at the end (Lys28 to Ala41). The areas at the begin and middle of the Aβ(1–42) peptide have an "antigenic potential". Taken the results together, it is suggested that the middle area has an "amyloidogenic potential" by forming noncovalent interactions between paired, antiparallel β-sheet conformations.

A perspective in drug research is to develop compounds that inhibit this hydrophobic core of monomeric Aβ peptides, blocking so the associations between the oligomeric β-strains. Quite recently, it was shown that a proline containing β-sheet blocker containing five amino acids in a typical random-coil conformation, is bound to Aβ(1–40) and Aβ(1–42), inhibiting thus amyloid formation [7, 9].

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