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Small Molecular Weight Compounds Antagonistic to Amyloid Peptide$_{25-35}$

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Abstract

High levels of the neurotoxic beta-amyloid protein (Aβ) in patients with Alzheimer's disease present a significant therapeutic target, although the protein is unlikely to be the sole instigator of this condition. Aβ initiates cell receptor and synapse dysfunction, and causes mitochondrial damage within neurons. Neurotransmitters and various small molecular weight compounds ameliorate the effects of Aβ on cell membranes. This study uses a molecular modeling technique to compare the structures of Aβ_{25-35} and compounds known to antagonize properties of the polypeptide. Compounds provide good fits to the peptide amino acid residues, revealing planarity in their linear structures and fitting points. Compounds and polypeptide share relative molecular similarity, affinity for receptors and apoptosis modulating properties indicative of their potential for competition at neuron membrane sites. The therapeutic targeting of Aβ by small molecular weight compounds may benefit from a multi-drug approach.

Keywords

Alzheimer's Disease, Beta-Amyloid Peptide, Beta-Amyloid Antagonists, Molecular Modeling

1. Introduction

In past decades, beta-amyloid protein (Aβ) has been a main focus of diagnostic and therapeutic strategies seeking to prevent the histological and neurochemical changes of Alzheimer's disease (AD) [1]. The 40 or more amino acid residues of Aβ contribute to an intrinsically disordered protein with changes in folding and conformation dependent on binding ligands and environment [2]. Aβ self-assembles on cell membranes disrupting receptor function and promoting the development of ion permeable pores [3] [4]. The resulting neurocytotox-

icity is manifest as oxidative-stress, changes in cell calcium and apoptosis [5]. Several classes of cell receptor are susceptible to desensitization, internalisation or activation by Aβ: adrenergic, NMDA and α7-nicotinic acid (α-7nACh) receptors [5] [6]. Aβ fragment A$\beta_{25\text{-}35}$, the biologically active region of Aβ, also inhibits glucose uptake in hippocampal neuron cultures via activation of Gs-protein coupled receptors [7].

The perceived role of Aβ in the causation of AD is currently more equivocal, as informed by a more recent body of experimental work on mouse models and the ineffectiveness of anti-amyloid therapies [8] [9]. Aβ may have a functional role in the brain, as it demonstrates concentration dependent beneficial effects on α-7nACh and NMDA receptors [10]. Picomolar concentrations of oligomeric Aβ modulate pre- and post-synaptic mechanisms, augmenting neurotransmitter release and facilitating early to late long-term potentiation (LTP) transition via α7-nAchR and the NO/cGMP pathway [11]. This more favourable view of Aβ complements the knowledge that platelets are a major source of amyloid precursor protein [12]. Amyloid fibril formation is a generic property of proteins, including β_2-microglobulin and proteins present in foods [13] [14].

There are endogenous defence mechanisms against the neurotoxicity of Aβ. α-7nAChRs are neuroprotective in regard to amyloid accumulation, cognitive decline and pathology in mice [15]. Insulin is one of several growth factors with impaired signaling in AD that provides protection following correction of its deficit in hippocampal neurons [16]. Steroids and cyclic nucleotides also have a role in regulating the toxicity of Aβ. Allopregnanolone restores learning and memory function in mice and reduces Aβ burden [17]. cAMP ameliorates Aβ induced memory impairment and hippocampal mitochondrial dysfunction in rats [18]. Studies in mice demonstrate a degree of interaction between Aβ and cGMP; down-regulation of cGMP signaling by Aβ, and cGMP enhancement of Aβ levels with positive effects on synaptic plasticity and memory [19]. Two studies on AD patients have reported reduced cerebrospinal fluid levels of cGMP (but not cAMP) in association with cognitive decline and amyloid pathology [20] [21].

Several drugs and natural products are known to interfere with the self-assembly and toxicity of Aβ. Doxocyclin [13], curcumin [22], resveratrol [23] and ibuprofen [24] are aggregation inhibitors of amyloid peptide and fibril formation. Tromethamine [25], valproic acid [26], cinnamaldehyde [27], vitamin E [28] and gallic acid [29] reduce the toxicity of A$\beta_{25\text{-}35}$. Docosahexaenoic acid, genistein and folic acid protect against A$\beta_{25\text{-}35}$-induced apoptosis [30] [31]. There is also epidemiologic evidence for delayed onset AD attributable to the use of NSAIDs [32]. Of pertinence to this study are observations that the above small molecular weight compounds modulate cell apoptosis and induce oxidative stress irrespective of the presence of Aβ [33]. This study uses a molecular modeling approach to report on molecular similarity within these compounds and the amino acid residues of A$\beta_{25\text{-}35}$. The results are relevant to the interaction of Aβ with cell

membrane receptors and antagonism of neurotoxicity by small molecular weight compounds.

2. Methods

The molecular structure and conformation of $A\beta_{25\text{-}35}$ is basedon the model given by Song [34]. The Nemesis software program (Oxford Molecular version 2.1) is used to build molecular structures from contents of the program fragment file and minimise the structures by conformational analysis. The compound structures are minimum energy conformers in an uncharged form, whereas polypeptide $A\beta_{25\text{-}35}$ is a partially minimised structure. The computational program fits paired molecular structures of the compounds and $A\beta_{25\text{-}35}$ on a three-point basis. Fitting points comprise of atoms of similar type and partial charge within compound and $A\beta_{25\text{-}35}$ structures, identified in the figures with respect to the amino acid labels. Compound colour-coded atoms in the figures identify ligand-fitting points: carbon-green, nitrogen-blue, oxygen-red. To improve on presentation, bond order within the molecular structures is not shown and in some fits of the compounds the $A\beta_{25\text{-}35}$ structure is cropped. The Nemesis program computes goodness-of-fit values, in respect of inter-atomic distance at each fitting point and root mean square (RMS) value.

3. Results

Compound fitting points are identified in **Figure 1** and **Figure 2** and the fitting data are given in **Table 1**. Neurotransmitter structures of NMDA, tromethamine and the α7-nAchR agonist TC-1698 fit to one amino acid residue (**Figure 1**). The structures of silibinin and cinnamaldehyde fit across two, whereas pregnenolone and folic acid fit across three residues (**Figure 2**). A second fit of NMDA to isoleucine residues is also given (**Figure 1(i)**). The fitting points of most compounds include a peptide bond carbonyl group, whereas nitrogen species are involved in the fit of folic acid. Several compounds fit to the same amino acid residues: cinnamaldehyde and gallic acid, NMDA and docosahexaenoic acid, ibuprofen and 17-β estradiol, folic acid and FDDNP (2-[1-[6-[2-fluroethyl(methyl)amino]napthalen-2-yl]ethylidene]propanedinitrile (a radiopharmaceutical used to disclose aggregates of $A\beta$ and tau) [1]. Valproic acid alone fits to methionine 35. The linear and planar dispositions of compound fitting points, evident within the figures, sometimes form part of a fused cyclic ring system as in doxycycline, 17-beta estradiol and pregnenolone. Comparative values for the compounds demonstrate good quality fits with interatomic distances of 0.16Å or less, and RMS values < 0.0300Å.

4. Discussion

Of approximately 100 agents currently in AD modification trials, 40% target amyloid and almost half are small molecular weight compounds [35]. Pharmacologic strategies that target intrinsically disordered proteins include disaggregation,

Table 1. Fitting data of compounds and β-amyloid$_{25\text{-}35}$ peptide.

Compound	Amino acid residues	Fitting points	Interatomic distances (Å)	RMS (Å)
Tromethamine	S26	O2C2O1	0.05, 0.03, 0.05	0.0134
Cinnamaldehyde	I32, G33	O1C1, C1'	0.08, 0.04, 0.10	0.0074
NMDA	N27	C1C2C4	0.03, 0.04, 0.02	0.0093
NMDA	I32, I31	C1', C1O1	0.10, 0.10, 0.01	0.0050
TC-1698	I31	C1C2C3	0.03, 0.04, 0.06	0.0054
Ibuprofen	I32, L34	O1C1, C4	0.04, 0.07, 0.05	0.0043
Gallic acid	I32, G33	O1C1, C1'	0.08, 0.05, 0.07	0.0093
Doxycyline	K28, N27	C1', C1C4	0.09, 0.11, 0.07	0.0261
Valproic acid	M35	O1C1C2	0.01, 0.01, 0.01	0.0022
Silibinin	I32, L34	O1C1, C1'	0.05, 0.14, 0.12	0.0050
Docosahexaenoic acid	I31, I32	C2C1, C1'	0.09, 0.14, 0.12	0.0116
Vitamin E	G33, L34	O1, C2C1	0.03, 0.10, 0.10	0.0051
17-β Estradiol	I32, L34	O1C1, C1'	0.06, 0.12, 0.06	0.0065
cGMP	K28, A30	O1C1, C1'	0.02, 0.04, 0.06	0.0004
Genistein	I31, L34	C2C1, C2'	0.08, 0.07, 0.03	0.0053
Curcumin	A30, G33	C2C1, C1'	0.15, 0.16, 0.02	0.0124
Pregnenolone	I31, I32, G33	C1C2C1'	0.04, 0.05, 0.06	0.0027
Folic acid	L34, G33, I32	N1C1N1'	0.11, 0.08, 0.08	0.0108
FDDNP	L34, G33, I32	C2C1C1'	0.06, 0.03, 0.04	0.0118
Cromoglycate-conformer	G29, L34	C1O1, C1'	0.11, 0.13, 0.02	0.0053

Compound molecular structures are superimposed and fitted individually to labeled amino acid residues of the peptide model (see **Figure 1**) by the molecular modeling program, generating fitting data and goodness of fit values.

and the promotion of a stable or non toxic species of amyloid protein [2]. Results from this study indicate that a planar pharmacophore incorporating oxygen-rich groups may afford a structural basis for the design of new compounds with the potential to interact with Aβ. Both features are present within a high energy cromoglycate conformer (2.5 kcal of free energy, **Figure 2**) but not in the folded minimum energy state conformer (not shown). The affinity of the compounds for different amino acid residues within A$\beta_{25\text{-}35}$ suggests that therapeutic targeting of Aβ may benefit from a multi-drug approach.

In regard to physiological properties of the investigated compounds, cinnamaldehyde reduces Aβ-induced toxicity in a neuronal cell line by interacting with adenosine and NMDA receptors [27]. Valproic acid and curcumin demonstrate neuroprotective properties against A$\beta_{25\text{-}35}$-induced oxidative damage and apoptosis in PC12 cell cultures [26] [36]. Docosahexaenoic acid and vitamin E have a synergistic effect in antagonising oxidative damage in PC12 cells induced

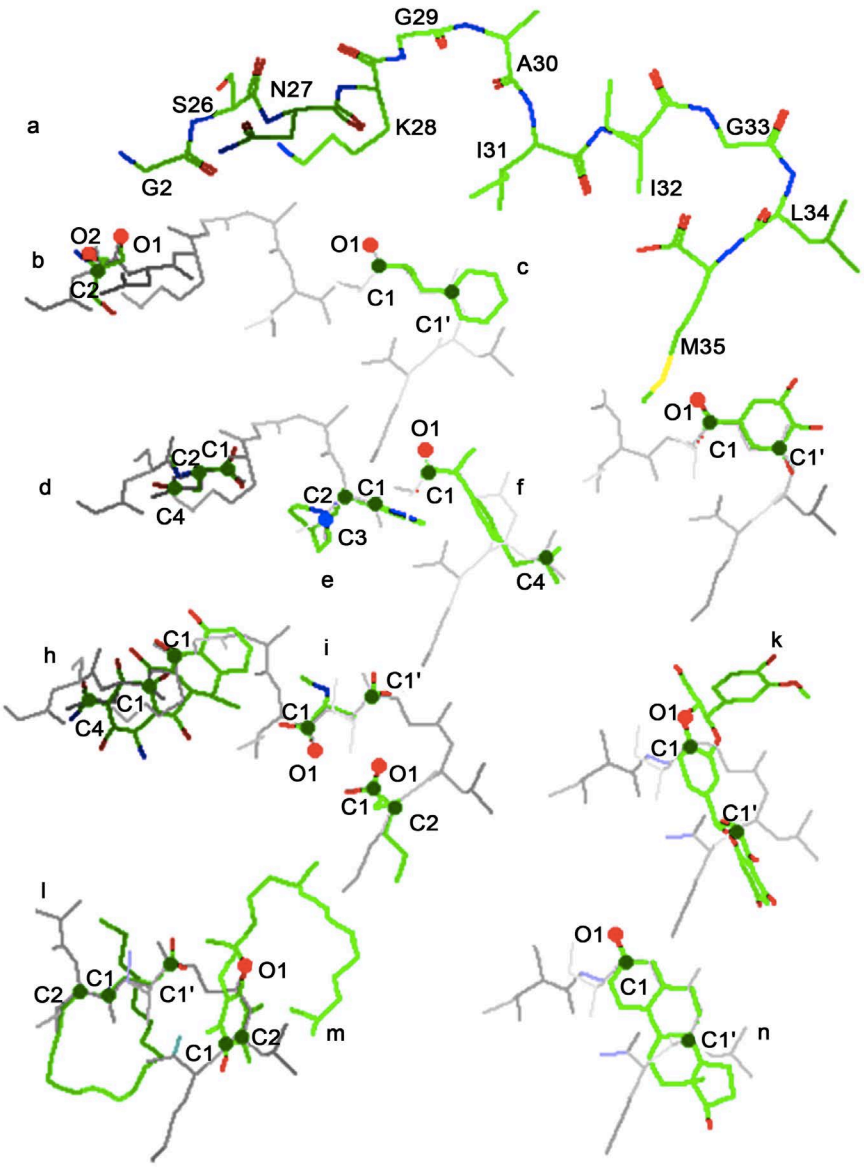

Figure 1. **a** Molecular model of A$\beta_{25\text{-}35}$ peptide with labeled amino acid residues: G-glycine, S-serine, N-asparagine, K-lysine, A-alanine, I-isoleucine, L-leucine, M-methionine. **b-n** Fits of compound structures to labeled fitting points of A$\beta_{25\text{-}35}$ peptide model(grey): carbon (green), nitrogen (blue), oxygen (red). **b** tromethamine, **c** cinnamaldehyde, **d** NMDA, **e** TC-1698, **f** ibuprofen, **g** gallic acid, **h** doxycyline, **i** NMDA, **j** valproic acid, **k** silibinin, **l** docosahexaenoic acid, **m** vitamin E, **n** 17-beta estradiol.

by A$\beta_{25\text{-}35}$ [28]. The inhibitory action of silibinin on ROS, induced by Aβ in a rat β-cell line, is attributed to up-regulation of estrogen receptor signaling [37]. Gallic acid improves spatial learning and memory in mice by disrupting A$\beta_{25\text{-}35}$ aggregation [29]. The destructive effects of doxycycline on amyloid fibril formation and cytotoxicity have been investigated using the β2-microglobulin protein [13]. Ibuprofen benefits the hippocampal region in rat brain by restoring Aβ impairment of the cGMP pathway and synaptic expression [24] [38]. Pregnenolone (but not the sulphate ester) provides protection against A$\beta_{25\text{-}35}$ toxicity in

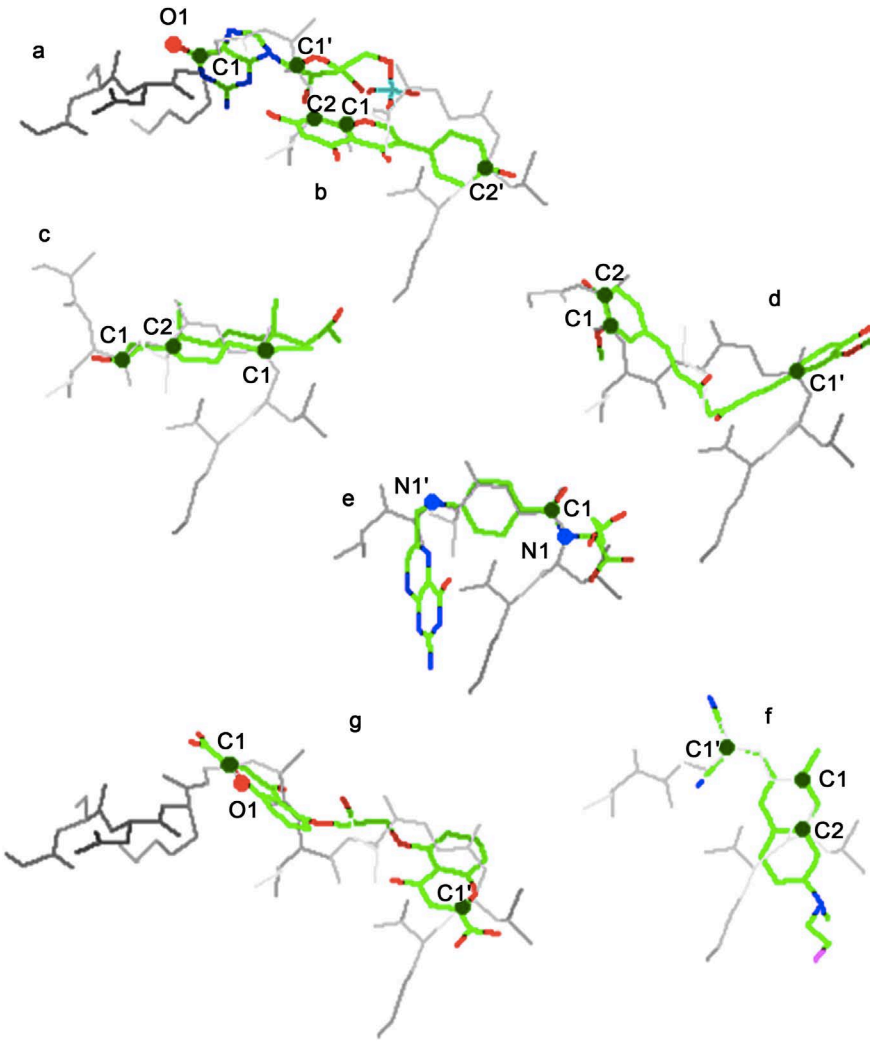

Figure 2. **a-g** Fits of compound structures to labeled fitting points of A$\beta_{25\text{-}35}$ peptide model (grey): carbon (green), nitrogen (blue), oxygen (red). **a** cGMP, **b** genistein, **c** pregnenolone, **d** curcumin, **e** folic acid, **f** FDDNP, **g** cromoglycate conformer.

PC-12 cell cultures [39]. In AD patients, pregnenolone sulphate and DHEAS levels are significantly reduced and correlate negatively with Aβ [40].

The changes within brain structure that produce the toxic environment and pathogenesis characteristic of AD are becoming more apparent. Reduced neurotransmitter and steroid levels are evident in AD patients and reported reductions in cyclic nucleotide synthesis may relate to these deficits, leading to loss of synapse function and neuron depletion [41] [42]. The normal G-protein cell cycle regulation of physiologic processes, responsive to neurotransmitters, cyclic nucleotides and steroid action, is diminished and superseded by abnormal ROS generation, amyloid production and cell apoptosis. Abnormalities within cell organelles, mitochondria and endoplasmic reticulum point to disordered metabolism and oxidative deficits. Aβ accumulates within mitochondria and inhibits processes within the respiratory chain [43]. Excess nitric oxide and reactive species of nitric oxide within mitochondria contribute to mitochondrial malfunction and neu-

ronal cell death [44]. The endoplasmic reticulum contributes to ROS production through the generation of disulphide bonds during protein-folding and -misfolding processes [45].

In the absence of pharmacologic intervention for AD, physical activity may prevent the decline in cognitive function, through assisting cerebral blood flow, neurogenesis and up-regulating neurotransmitter activity [46] [47]. Increases in synaptic activity and receptor expression protect against Aβ-associated impairment of synapse function [16] [48]. The population density of plasma membrane NMDA and AMPA receptors regulates the dysfunctional effects of Aβ at hippocampal neuron synapses [49] [50]. Deficits in neurotransmitter-targeted receptors facilitate the binding of Aβ to cell membrane receptors and internal access to cells [51].

A$\beta_{25\text{-}35}$ and the investigated compound structures share an affinity for cell membrane receptors, apoptosis modulation and relative molecular similarity. Although there are several compounds that reduce the toxic and apoptotic properties of Aβ, the focus should perhaps be on the function of the brain's endogenous steroids and cyclic nucleotides that contribute to this role in healthy individuals. In consideration of the available evidence for the functional roles of Aβ in neuronal and haemodynamic regulation, the initiation of apoptosis by Aβ may also be a natural function of this protein, targeting neurons with deficits in agonist and synaptic activity; eliminating cells that are no longer functional.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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