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## Letters

### Per-6-substituted-per-6-deoxy $\beta$ -cyclodextrins Inhibit the Formation of $\beta$ -Amyloid Peptide Derived Soluble Oligomers

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**Abstract:** Recent studies have indicated that the most important role of  $\beta$ -amyloid peptide ( $A\beta$ ) in the etiology of Alzheimer's disease may not be in plaque formation but in the formation of soluble, metastable  $A\beta_{1-42}$  neurotoxic intermediates (called ADDLs). In the present work we describe the preparation of per-6-amino-6-deoxy- $\beta$ -cyclodextrins, which inhibit ADDLs formation in vitro.

Alzheimer's disease (AD) is the most common cause of dementia in older individuals, affecting 5–10% of the population over the age of 65, and is characterized by a progressive deterioration in cognitive performance. It has long been proposed that the neurodegeneration in AD may be caused by deposition of amyloid  $\beta$ -peptide ( $A\beta$ ) in the plaques found in brain tissue.<sup>1,2</sup> However, a frequently voiced objection to this hypothesis is the fact that the number of amyloid deposits in the brain do not correlate well with the degree of cognitive impairment.<sup>3</sup> This is frequently recapitulated in hAPP transgenic mice models of AD,<sup>4,5</sup> where cognition deficits are observed in advance of amyloid deposition.<sup>6–8</sup>

In a recent review, Hardy and Selkoe analyze the known data concerning  $A\beta$  and conclude that in the early stages of AD the molecular species responsible for

neurological dysfunction appear to be small oligomeric assemblies of  $A\beta$ , termed ADDLs ( $A\beta$ -derived diffusible ligands), rather than the large insoluble fibrils found in amyloid plaques.<sup>9</sup> The soluble species form at lower  $A\beta_{1-42}$  concentrations, are metastable, and cause subtle injury to cultured neurons.<sup>10,11</sup>

Recently, we have shown the elevation of ADDLs in the brains of AD patients.<sup>12</sup> Further, microinjection into living rats of culture medium containing naturally secreted human  $A\beta$  revealed that oligomers in the absence of monomer and amyloid fibrils can inhibit long-term potentiation in the hippocampus, which was attributable specifically to the soluble oligomers of  $A\beta$ .<sup>13</sup>

As such, direct interference with the assembly or activity of ADDLs represents a highly attractive strategy for the potential treatment of AD. Papadopoulos and co-workers have recently shown that *Ginkgo biloba* extracts inhibit  $\beta$ -amyloid-induced cell death by inhibiting the formation of ADDLs,<sup>14</sup> but beyond this, little is known about agents that might act in this fashion.

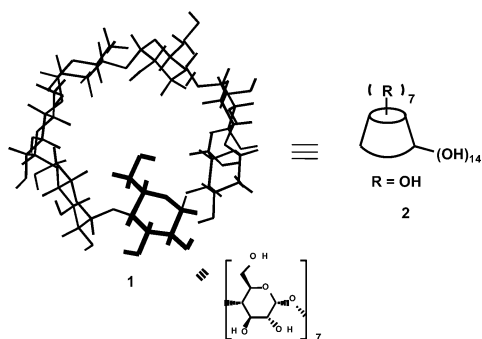
An interesting study by Camilleri and co-workers showed that  $A\beta$  interacts with  $\beta$ -cyclodextrin ( $\beta$ -CD), which diminishes substantially the neurotoxic effects of  $A\beta_{1-40}$  in PC12 cells.<sup>15</sup> In addition, Waite et al. have demonstrated the protective effects of  $\beta$ -CD in vivo.<sup>16</sup> We examined the effect of  $\beta$ -CD on the ability to inhibit ADDLs formation but found little effect on the formation of the soluble forms of this neurotoxin. Nevertheless, we had previously shown what appeared to be specific interactions of per-6-substituted- $\beta$ -CD libraries with other small molecules,<sup>17,18</sup> which prompted us to examine several of these libraries for their ability to inhibit ADDLs formation.<sup>19</sup>

Using a high-throughput dot blot assay recently developed in our laboratories for measuring  $A\beta$  oligomerization,<sup>20</sup> we describe herein the evaluation of certain  $\beta$ -CD amino derivatives ( $\beta$ -ACDs) from these library mixtures which inhibit the oligomerization of  $A\beta_{1-42}$ .  $\beta$ -CD (**1**) is a cyclic  $\alpha$ -1,4-linked glucopyranose oligomer (Figure 1) whose shape is reminiscent of a lampshade, frequently depicted as in **2**. There are three different hydroxyls for each sugar in the  $\beta$ -CD molecule

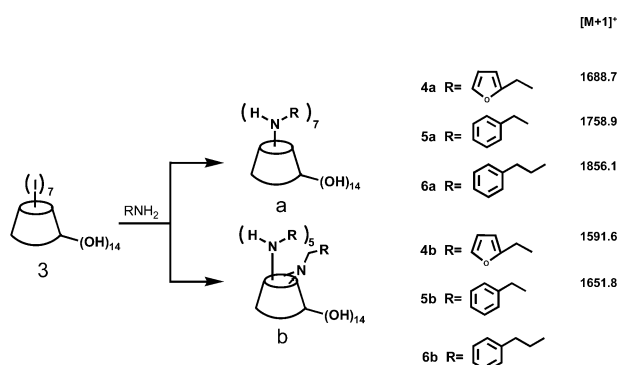
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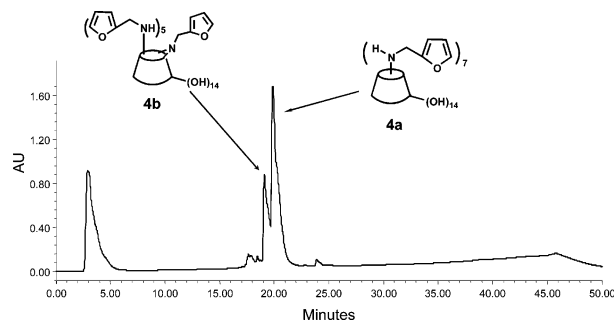
**Figure 1.**  $\beta$ -Cyclodextrin ( $\beta$ -CD) structure.



**Figure 2.** Synthesis of  $\beta$ -ACD derivatives. Derivatives were prepared by treatment of periodo-per-6-deoxy- $\beta$ -CD **3** with amine. Preparative reversed-phase HPLC provided the homogeneous per-substituted derivatives **a** in addition to cross-linked derivatives **b**, with observed singly charged ESMS ions as indicated. See text for details.

that can be readily differentiated chemically: the primary face 6-hydroxyls and the secondary face 2- and 3-hydroxyls. There is no plane of symmetry in this toroidal molecule, resulting in the nonequivalence of the primary hydroxyl groups on substitution. The end result of these structural features is that symmetry operations are not possible with different substitution patterns and each pattern represents a different compound. This asymmetry frequently gives rise to closely related compounds that are difficult to separate and also greatly complicates the spectral interpretation in all but the per-substituted derivatives.

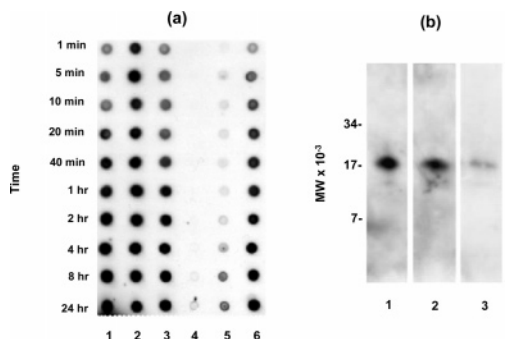
Per-6-substituted- $\beta$ -CDs were prepared under nitrogen by treating a solution of per-6-iodo- $\beta$ -cyclodextrin (**3**, 300 mg, 0.157 mmol) with benzylamine or furfurylamine (3 mL) at room temperature for 120 h and then heating at 80–85 °C for 6 h (Figure 2). After the removal of excess amine under reduced pressure at room temperature, the residue was solidified with ethyl acetate. The solid was filtered, ultrasonicated in ethyl acetate, and then filtered and dried to give the crude products as off-white powders. Analytical HPLC ( $C_{18}$  column 3.9 mm  $\times$  15 mm, 4  $\mu$ m; solvent, (A) water/0.1% TFA, 3% MeOH (B)  $CH_3CN$ /0.1% TFA, 3% MeOH, linear gradients (A to 92% B over 40 min, then to 95% B over 5 min) at 0.5 mL/min) gave two major peaks for the furfurylamine (18.6, 19.7 min) and benzylamine  $\beta$ -ACD (21.6, 23.1 min) products. Figure 3 shows an example of an HPLC chromatogram of the products produced in these reactions, here for the furfurylamine derivatives. Preparative reversed-phase HPLC ( $C_{18}$  column 15 mm  $\times$  300 mm, 100 Å, ca. 20 mg loading) provided near-baseline separation of these active anti-ADDLs agents



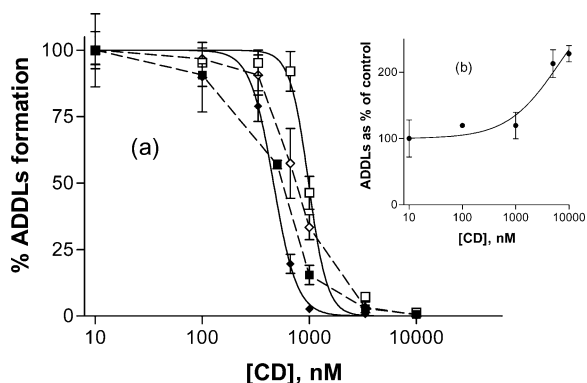
**Figure 3.** Representative reversed-phase HPLC chromatogram of reaction products from periodo-6-deoxy- $\beta$ -CD and furfurylamine. See text for chromatography details.

in both cases as evidenced by analytical reversed-phase chromatography. Each of the four products were subjected to ESMS and  $^{13}C$  and  $^1H$  NMR analyses. These NMR data were fully consistent with the proposed structures for the per-substituted-per-6-deoxy- $\beta$ -ACDs **4a** and **5a**. In addition, the ESMS of these derivatives showed  $[M + H]^+$  ions (and doubly charged ions) consistent with the proposed structures (Figure 2). We have since confirmed that these compounds can be prepared relatively free of the cross-linked product using per-6-deoxy-per-6-bromo- $\beta$ -CD as previously described.<sup>21–23</sup> The mass of the second HPLC peak in both cases suggested that after six nucleophilic displacements of the iodine, there was an internal displacement to give the cross-linked products **4b** and **5b**. However, the NMR data for the proposed **4b** and **5b** were not fully interpreted because of the multiplicity of signals caused by the asymmetry in the molecule. By use of the same procedures for preparation and purification, the per-6-substituted phenethyl derivative **6a** (26.1 min retention time under the same analytical HPLC conditions described above) was also prepared and tested.

For an ADDLS assay, an aliquot of  $A\beta_{1-42}$  was dissolved in anhydrous DMSO to a concentration of 22.5 mg/ $\mu$ L (5 mM), pipet-mixed, and further diluted into ice-cold F12 medium (phenol red free) (Biosource CA) to make a 0.5  $\mu$ M stock solution. For each experiment, 4  $\mu$ L of the 0.5  $\mu$ M  $A\beta$ -DMSO stock solution was added to 196  $\mu$ L of each  $\beta$ -CD sample solution, rapidly mixed, and incubated at 4 °C, with a final  $A\beta$  concentration of 10 nM. Dot-blot imaging was used to monitor ADDLs formation; for a complete description of this assay, see Chang et al.<sup>20</sup> At the indicated time point, aliquots (2  $\mu$ L) of each solution were applied to a nitrocellulose membrane, which was prewetted with 20 mM Tris-HCl, pH 7.6, and 137 mM NaCl (TBS) and partially dried. The nitrocellulose membranes were then blocked in 0.1% Tween 20 in TBS (TBS-T) with 5% nonfat dry milk for 1 h at room temperature. The samples were incubated for 1 h at room temperature with primary anti-ADDLs polyclonal antibody M93-3 in the blocking buffer (1:1000), washed 3  $\times$  15 min with TBS-T, followed by addition of HRP-conjugated antirabbit antibody (1:50000, Amersham).<sup>24</sup> Antibody binding was visualized with a SuperSignal ECL kit (Pierce) and analyzed with the 440CF imaging station (Kodak) (Figure 4). In selected cases, Western blots were run to verify ADDLs species, whereby 20  $\mu$ L aliquots of incubation mixtures were subjected to SDS-PAGE and separated on a 16.5%



**Figure 4.** Dot-blot and Western-blot ADDLs assays. (a) Dot-blot assays were performed to measure ADDLs formation over 24 h. Assays were performed on reaction products containing persubstituted  $\beta$ -ACDs as major component and cross-linked derivative as minor components (see Figure 2): (1) control; (2) imidazole- $\beta$ -CD products at 20  $\mu$ M; (3) *N,N*-dimethylethylenediamine- $\beta$ -CD products at 20  $\mu$ M; (4–6) furfurylamine- $\beta$ -CD products at 20, 2, and 0.2  $\mu$ M, respectively. (b) Western blots of ADDLs after 4 h of incubation: (1) control; (2)  $\beta$ -CD; (3) furfurylamine- $\beta$ -CD products at 20  $\mu$ M. For further details, see text.



**Figure 5.** Concentration-dependent inhibition of ADDLs formation with purified  $\beta$ -ACD derivatives. (a) Inhibition of ADDLs formation by densitometric measurement of dot-blot assays at 4 h for purified  $\beta$ -ACDs: ■, **4a**; □, **4b**; ◆, **5a**; ◇, **5b**. (b) Increase in ADDLs formation with purified phenethylamine  $\beta$ -ACD **6a**. Data were normalized to 100% ADDLs formation at 10 nM  $\beta$ -ACD and show standard error of the mean.

Tris-tricine gel (Bio-Rad), transferred to nitrocellulose, and probed with antibodies as described above.<sup>24</sup>

Several control incubations were run to exclude the possibility that  $\beta$ -ACDs interact directly with M93. For example, (a) ADDLs were preformed over 24 h and then treated with  $\beta$ -ACD and (b) ADDLs were applied to nitrocellulose followed by application of  $\beta$ -ACD to the blot before application of the M93 antibody. In both cases,  $\beta$ -ACD caused no perturbation of the immunoblot response. Incubations were carried out at 4 °C to maximize response and to allow kinetic analysis of ADDLs formation via dot-blot, which is not possible at 37 °C.

Concentration–response curves were prepared by carrying out dot-blot assays with  $A\beta_{1-42}$  (10 nM) in the presence of purified  $\beta$ -ACDs at the indicated concentrations. The response was determined at 4 h using the Kodak 1D imaging software as shown in Figure 5. Fitting of curves at other time points yields similar  $EC_{50}$  values.

ADDLs oligomers are formed from aggregation of  $A\beta$  at physiological concentrations (10 nM).<sup>5</sup> The anti-

ADDLs antibody, M93-3, has been shown to be sensitive and selective for Western blot analysis of ADDLs tetramers at loadings as low as 0.1 fmol; at higher loadings, bands for trimer but not for monomer were observed.<sup>20,24</sup> Current theories on  $A\beta$  self-assembly posit a crucial role for hydrophobic/electrostatic interactions in the  $A\beta_{16-20}$  motif (KLVFFA).<sup>25</sup> Hydrophobic recognition by the CD cavity is well described.<sup>26</sup> Therefore, ACDs represent rational candidates for inhibitors of ADDLs formation, since the cationic annulus, hydrophobic corona, and cavity provide the required hydrophobic/electrostatic binding.<sup>27</sup> Similarly,  $\beta$ -ACD libraries represent a rational choice for initial probing of ADDLs inhibition because of the diversity provided by the inherent asymmetry of  $\beta$ -CD.

In a previous report,<sup>19</sup> we described the preparation and testing of libraries of per-6-substituted- $\beta$ -ACDs for their ability to inhibit ADDLs formation. The libraries were prepared from per-6-iodo-per-6-deoxy- $\beta$ -CD by direct displacement with amine nucleophiles, used in combinations of three. The choice of the more reactive per-iodo- $\beta$ -CD rather than the per-bromo- $\beta$ -CD was made to enhance the statistical distribution of the amine groups on the face of the cyclodextrin molecule. By examination of several of these libraries (each based on a statistical distribution containing about 2000 derivatives), there was indication that the inhibitory activity was a function of the type of amine used for preparation of the particular library. The most active library tested was derived from the combination of imidazole, *N,N*-dimethylethylenediamine, and furfurylamine, which at 20  $\mu$ M total library inhibited ADDLs formation from  $A\beta_{1-42}$  (10 nM).<sup>19,20</sup>

The  $\beta$ -ACD libraries represent complex mixtures of  $\beta$ -ACD isomers (and side products from the reaction), which allowed selection of preferred amine side chains for synthesis of  $\beta$ -ACDs produced from the displacement with amines used individually as nucleophiles. We found that  $\beta$ -ACD products from the reaction with furfurylamine had significant activity (Figure 4a, lanes 4–6) while those from imidazole (Figure 4a, lane 2) and *N,N*-dimethylethylenediamine (Figure 4a, lane 3) resulted in almost no activity. As shown in the Western blot assay of Figure 4b, this activity appears to largely inhibit the tetrameric form of the ADDLs (18 056 Da). This led us to explore further the  $\beta$ -ACD displacement products (analyzed by ESMS) from a variety of individual amine side chains in reaction with the per-iodo- $\beta$ -CD for inhibition of ADDLs formation.

Reaction products with all aliphatic amines tested showed no detectable activity. On the other hand, aromatic side chain reactants tended to show highly variable activity. Thus, whereas the benzylamine products showed significant inhibition at 2  $\mu$ M (based on the MW of the per-substituted product),  $\beta$ -CD products from the reaction with pyridine were essentially inactive. Further, reaction products with phenethylamine had diagrammatically the opposite effect, i.e., resulting in stimulation of ADDLs formation (Figure 5b). Similarly, the structure was observed to strongly influence activity in the furfurylamine series, with the furfurylamine  $\beta$ -ACD itself showing good activity. However, placing a methyl group on the furan ring led to reduced activity, while a methyl group on the nitrogen gave products with

activity comparable to that of the parent furfurylamine  $\beta$ -ACD. Finally, saturation of the furfurylamine ring dramatically reduced the ability of these derivatives to inhibit ADDLs formation and in fact, like the phenethylamine, appeared to enhance ADDLs formation relative to controls.

The best conditions for preparation of the per-substituted derivatives were to treat the per-iodo- $\beta$ -CD with the side chain neat for 2 days at room temperature and then increase the temperature to 80–85 °C for 6 h. Initially, the aforementioned testing was carried out on crude products because  $\beta$ -CD derivatives are notoriously difficult to separate, as previously noted. Nevertheless, ESMS and in some cases LCMS analyses of these reaction mixtures indicated that the per-substituted  $\beta$ -ACD was the major product with partially substituted isomers a very minor component. In addition, there was always a slower running peak (ca. 10% of the major per-substituted peak) whose mass suggested a six substitution pattern with one of the six amines in a tertiary form spanning two positions (probably adjacent) on the primary  $\beta$ -CD face. A typical HPLC chromatogram for the products is shown in Figure 3 for the furfurylamine derivative. The aforementioned reaction conditions maximized the per-substituted derivatives, but never gave products free from these side reactions. The purified components of the two most inhibitory products (i.e., those from the reaction of per-iodo- $\beta$ -CD with furfurylamine and benzylamine) were selected for isolation and assay.

Attempts to separate the two major products by flash chromatography on silica gel were only partially successful. However, a preparative reversed-phase HPLC separation of the per-substituted  $\beta$ -ACD produced chromatographically homogeneous products in the case of the per-6-benzylamine  $\beta$ -CD **5a**, its putative cross-linked derivative **5b**, the per-6-furfurylamine  $\beta$ -CD **4a**, and its putative cross-linked derivative **4b**. These purified derivatives were subjected to full concentration–response analyses in the ADDLs dot-blot assay (Figure 5a), yielding IC<sub>50</sub> values of 0.54, 1.0, 0.46, and 0.76  $\mu$ M for the  $\beta$ -ACDs **4a**, **4b**, **5a**, and **5b**, respectively.

The anti-ADDLs activity appears to be saturable, as indicated by the sigmoidal concentration–response curves, and specific, since corresponding concentrations of  $\beta$ -CD itself or the free side chain amines did not show any detectable inhibitory activity under the same conditions. In addition, whereas the per-6-benzylamine  $\beta$ -ACD **5a** was inhibitory for ADDLs, the corresponding per-6-phenethylamine  $\beta$ -ACD **6a** shows dramatically the opposite effect (Figure 5b). Thus, at about 5 times the concentration of the inhibitory effect of its benzylamine counterpart, the phenethylamine derivatives causes a greater than 200% increase in ADDLs formation relative to control.

We are presently exploring derivatization to obtain  $\beta$ -ACDs that are more potent and more lipophilic with increased membrane permeability as a potential means of controlling in vivo ADDLs formation in the treatment of AD.

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