Inhibition of metal-induced amyloid β-peptide aggregation by a blood–brain barrier permeable silica–cyclen nanochelator

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Alzheimer’s disease (AD) is a neurodegenerative malady associated with amyloid β-peptide (Aβ) aggregation in the brain. Metal ions play important roles in Aβ aggregation and neurotoxicity. Metal chelators are potential therapeutic agents for AD because they could sequester metal ions from the Aβ aggregates and reverse the aggregation. The blood–brain barrier (BBB) is a major obstacle for drug delivery to AD patients. Herein, a nanoscale silica–cyclen composite combining cyclen as the metal chelator and silica nanoparticles as a carrier was reported. silica–cyclen was characterized by scanning electron microscopy (SEM), transmission electron microscopy (TEM), Fourier transform infrared (FT-IR) and dynamic light scattering (DLS). The inhibitory effect of the silica–cyclen nanochelator on Zn²⁺ or Cu²⁺ induced Aβ aggregation was investigated by using a BCA protein assay and TEM. Similar to cyclen, silica–cyclen can effectively inhibit the Aβ aggregation and reduce the generation of reactive oxygen species induced by the Cu–Aβ₄₀ complex, thereby lessening the metal-induced Aβ toxicity against PC12 cells. In vivo studies indicate that the silica–cyclen nanochelator can cross the BBB, which may provide inspiration for the construction of novel Aβ inhibitors.

Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder affecting the memory and cognitive functions of the brain.¹ Although the molecular mechanism of AD pathogenesis is not clearly understood, much research has demonstrated that polymerization of amyloid β-peptides (Aβ) into amyloid fibrils is a critical step in the pathogenesis.² The pathological hallmark of AD is the aggregation of Aβ, predominantly Aβ₄₀ and Aβ₃₂ generated from the amyloid precursor protein (APP), which lead to the formation of oligomers and neuritic plaques in the brain.³,⁴ Metal ions, such as Zn⁵⁺, Cu²⁺ and Fe³⁺, play important roles in the Aβ aggregation and neurotoxicity, because they can readily induce Aβ nucleation and facilitate the formation of neurotoxic reactive oxygen species (ROS).⁵ Thus, metal chelation therapy has been extensively studied as a treatment for AD, which can block the formation of ROS and reduce the Aβ aggregation induced by metal ions.⁶

Although much research has been directed to the development of AD therapy,⁷–¹⁰ effective treatments are still unavailable. One of the major reasons is that most of the drug candidates are unable to cross the blood–brain barrier (BBB),¹¹,¹² which is formed primarily by endothelial cells that line the cerebral microvasculature and surrounding perivascular elements.¹³ Adjacent endothelial cells form complex tight junctions, creating a physical barrier which severely limits the paracellular transport across the BBB.¹⁴ The BBB allows for the passive diffusion of small lipophilic molecules, whereas limits the passive permeation of hydrophilic substances or molecules with high molecular weight.¹⁵ Since only lipophilic drugs with a molecular weight less than 450 Da can cross the BBB, most of the traditional drug candidates do not meet this requirement.¹⁶

In an attempt to overcome the above limitations, nanocarriers have been investigated as drug delivery vehicles to the central nervous system (CNS).¹⁷–²⁰ The mesoporous silica (SiO₂) nanoparticles can be utilized to carry various drugs and other functional agents due to their unique properties such as large surface area, stable aqueous dispersion, none toxicity, easy surface modification, excellent biocompatibility and in vivo biodegradability.²¹–²³ The organically modified SiO₂ nanoparticles have been used as efficient non-viral vectors to delivery gene therapeutic agent into the CNS in vivo.²⁴ We and other researchers ever reported that macrocyclic chelator 1,4,7,10-tetraazaacyclodecane (cyclen) could reduce the
metal-induced Aβ aggregation and neurotoxicity.\textsuperscript{25,26} However, the hydrophilic cyclen (water solubility: 999 g L\textsuperscript{-1}) may be hard to cross the BBB.

In this study, we designed a novel nanoscale chelator SiO\textsubscript{2}–cyclen, which conjugated SiO\textsubscript{2} nanoparticles as delivery carriers with cyclen as a metal chelator, for inhibiting the metal-induced Aβ toxicity (Scheme 1). The effect of SiO\textsubscript{2}–cyclen nanochelator on Aβ aggregation and neurotoxicity, as well as its BBB permeability were investigated \textit{in vitro} and \textit{in vivo}.

**Results and discussion**

**Synthesis and characterization of SiO\textsubscript{2}–cyclen**

SiO\textsubscript{2}–cyclen nanochelator was designed and fabricated according to a modified literature method.\textsuperscript{27} Cetyltrimethylammonium bromide (CTAB) was used as the cationic surfactant, tetraethylorthosilicate (TEOS) was served as the silica source, and ammonium hydroxide was used as the catalyst. In order to attach the metal chelator cyclen on the surface of SiO\textsubscript{2} nanoparticles, 3-chloropropyltriethoxysilane was used as a linker to fabricate the nanoscale SiO\textsubscript{2}–cyclen chelator. The morphology of the acquired SiO\textsubscript{2}–cyclen nanochelator was characterized by SEM (Fig. 1A) and TEM (Fig. 1B). The particles are spherical in shape and their size was smaller than 100 nm, which may enter the cells readily under fluid flow conditions.\textsuperscript{28} The average hydrodynamic diameter of SiO\textsubscript{2}–cyclen particles was determined by dynamic light scattering, which give a mean diameter of 65.2±4.9 nm (DLS, Fig. 1C). The size of particles is just within the dimension range (40–100 nm) of nanoparticles that is not only suitable for drug carriers and cellular uptake,\textsuperscript{29} but also suitable for transporting drugs across the BBB.\textsuperscript{30} In the FT-IR spectra, the peak at 1079 cm\textsuperscript{-1} is attributed to the bond of Si–O, and those at 2931, 1460, 1353 cm\textsuperscript{-1} are attributed to the bonds of C–H, N–H, C–N, respectively (Fig. 1D). The relative intensity of C–H and N–H increases as the functionalization goes deeper; by contrast, that of Si–O fluctuates. The changes manifest that cyclen has been linked to the surface of SiO\textsubscript{2} nanoparticles. The results indicate that the SiO\textsubscript{2}–cyclen nanochelator exists in single particles and disperses separately in aqueous suspension.

**Chelation with Cu\textsuperscript{2+} or Zn\textsuperscript{2+}**

Cyclen is a metal chelator and has potential to disaggregate the metal-induced Aβ aggregates as previously reported.\textsuperscript{25,26,31} The chelating ability of SiO\textsubscript{2}–cyclen nanochelator was determined by ICP-MS after incubation with Cu\textsuperscript{2+} and Zn\textsuperscript{2+}. The Cu and Zn amounts after reacting with SiO\textsubscript{2}–cyclen were 22.18±0.33 and 22.48±0.29 μg mg\textsuperscript{-1} in terms of SiO\textsubscript{2}–cyclen weight, respectively. As a control, no Cu and Zn was detected in SiO\textsubscript{2}–Cl. The results indicate that cyclen tethered to the surface of SiO\textsubscript{2} nanoparticles still retains the chelating ability to Cu\textsuperscript{2+} and Zn\textsuperscript{2+}.

**BCA protein assay**

The effect of SiO\textsubscript{2}–cyclen nanochelator on the Zn\textsuperscript{2+}- or Cu\textsuperscript{2+}-induced Aβ aggregation was investigated by measuring the percentage of soluble Aβ in the supernatant of the reaction.

\[ \text{Percentage of soluble Aβ} = \frac{\text{Soluble Aβ in supernatant}}{\text{Total Aβ}} \times 100\% \]

**Fig. 2.** Percentage of soluble Aβ in the solution containing Zn\textsuperscript{2+} or Cu\textsuperscript{2+} with or without SiO\textsubscript{2}–cyclen after incubation at 37 °C for 24 h. (A) Aβ; (B) Aβ + M\textsuperscript{2+}; (C) Aβ + M\textsuperscript{2+} + SiO\textsubscript{2}–cyclen; (D) Aβ + M\textsuperscript{2+} + SiO\textsubscript{2}–Cl; (E) Aβ + M\textsuperscript{2+} + cyclen. M\textsuperscript{2+} = Cu\textsuperscript{2+} or Zn\textsuperscript{2+}, pH = 7.4, [Aβ\textsubscript{40}] = 40 μM, [Aβ\textsubscript{40}] : [M\textsuperscript{2+}] : [chelator] = 1 : 2 : 2.
mixtures, with SiO₂–Cl and cyclen as the references. As shown in Fig. 2, Aβ₄₀ is almost completely soluble in the absence of metal ions and chelators. However, soluble Aβ in the supernatant of Aβ reaction mixtures containing Zn²⁺ or Cu²⁺ decreases to 10% and 24%, respectively, indicating that most Aβ is aggregated and deposited by metal ions. In the presence of SiO₂–cyclen, the solubility of Aβ increases obviously, suggesting that the SiO₂–cyclen nanochelator can inhibit the metal-induced aggregation of Aβ. As a comparison, SiO₂–Cl can hardly inhibit the metal-induced Aβ aggregation. These results show that the cyclen-modified mesoporous silica nanoparticles still have metal-chelating function and can inhibit the metal-induced Aβ aggregation.

Inhibition of ROS generation

Redox-active metal ions are crucial for the production of ROS and oxidative stress. Aβ could promote the production of ROS in the presence of redox-active metal ions, leading to pathological oxidative stress in AD. Chelating agents can reduce the generation of ROS through removing Cu²⁺ ions from the Cu–Aβ complex. The generation of ROS induced by the Cu–Aβ complex was monitored using 2′,7′-dichlorofluorescin diacetate (DCFH-DA). DCF is a fluorescent marker derived from the reaction of nonfluorescent DCFH with ROS in the presence of horseradish peroxidase (HRP). The fluorescence intensity of DCF correlates with the amount of reactive oxygen radicals. As shown in Fig. 3, strong fluorescence of DCF is measured at 522 nm for the Cu–Aβ₄₀ system without the SiO₂–cyclen nanochelator (b); in the presence of SiO₂–cyclen, the fluorescence intensity decreases obviously (e). The results indicate that SiO₂–cyclen can reduce the generation of ROS induced by the Cu–Aβ₄₀ complex. In contrast, SiO₂–Cl shows no effect on the reduction of ROS (d), because it does not coordinate with the Aβ-bound Cu²⁺ and hence can hardly influence the Cu–Aβ₄₀-mediated redox chemistry. These results indicate that the SiO₂–cyclen nanochelator reduces the production of ROS induced by Cu–Aβ complex almost as effectively as cyclen.

Morphology changes of Aβ aggregates

Negative staining TEM was exploited to investigate the effect of the SiO₂–cyclen nanochelator on the morphology of metal-induced Aβ aggregates. The images of Zn²⁺- or Cu²⁺-induced Aβ aggregates in the absence and presence of the nanochelator are shown in Fig. 4. Only long unbranched fibrils, a typical structure for amyloid fibrils, were observed in the solution of Aβ₄₀ (Fig. 4A). However, after Zn²⁺ or Cu²⁺ was added, large amounts of amorphous aggregates were formed in the solution of Aβ₄₀ (Fig. 4B and C), which are consistent with our previous observations. In the presence of SiO₂–cyclen, the metal-induced Aβ₄₀ aggregates were almost disappeared, and the morphology of the samples was similar to that of Aβ₄₀ samples (Fig. 4D and G). Cyclen also inhibited the Zn²⁺- or Cu²⁺-induced Aβ₄₀ aggregation and made the morphology similar to that of Aβ₄₀ alone (Fig. 4F and I). More aggregates were observed in the presence of SiO₂–Cl owing to its inability to chelate Zn²⁺ or Cu²⁺ (Fig. 4E and H). The results indicate that the SiO₂–cyclen nanochelator can inhibit the Zn²⁺- or Cu²⁺-induced Aβ₄₀ aggregation.

Inhibition of neurotoxicity

The neurotoxicity of Zn²⁺- or Cu²⁺-Aβ₄₀ complexes against PC12 cells was investigated by the MTT assay. The inhibition of SiO₂–cyclen nanochelator against the Aβ₄₀-induced neurotoxicity was shown in Fig. 5, with cyclen and SiO₂–Cl as the references. Aβ₄₀ in the presence of Zn²⁺ or Cu²⁺ was quite toxic to the rat pheochromocytoma PC12 cells (cell viability is about 70%), while Zn²⁺, Cu²⁺, and Aβ₄₀ alone are almost nontoxic. In the presence of SiO₂–cyclen, the cell viability in the Zn²⁺–Aβ₄₀ system increased from 74% to 91%, and that in the Cu²⁺–Aβ₄₀ system increased from 71% to 93%, respectively. Interestingly, SiO₂–cyclen and its Zn²⁺ or Cu²⁺ complex is nontoxic toward the cells. In the presence of SiO₂–Cl, the cell viability is similar to that in the presence of Aβ₄₀ and Zn²⁺ or Cu²⁺, indicating that SiO₂–Cl had no effect on the neurotoxicity of the Zn²⁺– or Cu²⁺–Aβ₄₀ complex. After incubating with cyclen, the cell viability was above 90%, even in the present of Zn²⁺– or Cu²⁺–Aβ₄₀ complex. These results demonstrate that the SiO₂–cyclen nanochelator can inhibit the neurotoxicity of Zn²⁺- or Cu²⁺-Aβ₄₀ complexes and enhance the viability of neuron cells.

![Fig. 3](image-url) Fluorescence of DCF (λₑ = 485 nm) reflecting the effect of SiO₂–cyclen on the production of H₂O₂ by the Cu–Aβ₄₀ complex. [Aβ₄₀] = 0.8 μM, [Cu²⁺] = [chelator] = 0.6 μM, [HRP] = 0.04 μM, [DCFH] = 100 μM, [ascorbate] = 10 μM, pH = 7.4.

![Fig. 4](image-url) TEM images of Aβ (A), Aβ + Cu²⁺ (B), Aβ + Zn²⁺ (C), Aβ + Cu²⁺ + SiO₂–cyclen (D), Aβ + Cu²⁺ + SiO₂–Cl (E), Aβ + Cu²⁺ + cyclen (F), Aβ + Zn²⁺ + SiO₂–cyclen (G), Aβ + Zn²⁺ + SiO₂–Cl (H), Aβ + Zn²⁺ + cyclen (I), respectively, after incubation at 37°C for 24 h. pH = 7.4, [Aβ₄₀] = 20 μM, [Aβ₄₀] : [M²⁺] : [chelator] = 1 : 2 : 2.
probably due to the metabolism of SiO2
penetrate the BBB of mice. The amount of Si decreased at 24 h
increased a
To evaluate the
Biochem Ltd. (China). Zinc acetate dehydrate, copper chloride,
trimethylamine (TEA), toluene, and HNO3 were purchased from
Cetyltrimethylammonium bromide (CTAB), ammonium
hydroxide, tetraethylorthosilicate (TEOS), isopropanol, 3-chloro-
opropyltriethoxysilane, 1,4,7,10-tetraazacyclododecane (cyclen),
hydroxide, tetraethylorthosilicate (TEOS), isopropanol, 3-chlor-
Table 1 The amount of silicon (μg g⁻¹) in C57BL/6J mice brain
determined by ICP-MS in terms of body weight pre- or post-injection
Pre-injection
Post-injection
6 h 12 h 24 h
5.42 ± 0.32 11.11 ± 0.41 13.09 ± 0.37 10.29 ± 0.34
diphenyl-2-H-tetrazolium bromide (MTT) were purchased from
Sigma-Aldrich. Micro BCA protein assay kit was purchased from
Beyotime biotech. Ltd. (China). All the aqueous solutions were
prepared using Milli-Q water and filtered through a 0.22 μm
filter (Millipore). Stock solutions of Aβ40, Cu²⁺, and Zn²⁺ were
prepared according to the reported procedures.

The scanning electron microscopy (SEM) images were ob-
tained using a Hitachi S-4800 high resolution SEM on the
conductivity of the SiO2–cyclen

Blood–brain barrier permeability
To evaluate the in vivo BBB permeability of the SiO2–cyclen
nanochelator, animal experiments were carried out by using
C57BL/6J mice. The amount of silicon in mice brain pre- or post-
injection of SiO2–cyclen was listed in Table 1. The amount of Si
increased after 6 h, thus suggesting that the nanochelator could
penetrate the BBB of mice. The amount of Si decreased at 24 h
probably due to the metabolism of SiO2–cyclen in vivo. The
SiO2–cyclen nanochelator may cross the BBB via the adsorptive
or receptor-mediated transportation, which is similar to the
situation of insulin, albumin and low density lipoprotein
receptor as reported previously.

Experimental
Materials and methods
Cetyltrimethylammonium bromide (CTAB), ammonium
hydroxide, tetraethylorthosilicate (TEOS), isopropanol, 3-chloro-
opropyltriethoxysilane, 1,4,7,10-tetraazacyclododecane (cyclen),
trimethylamine (TEA), toluene, and HNO3 were purchased from
J&K Ltd. (Beijing, China). Human Aβ40 was purchased from GL
Biochem Ltd. (China). Zinc acetate dehydrate, copper chloride,
2',7'-dichloro-fluorescein diacetate (DCFH-DA), tris(hydrox-
ymethyl)aminomethane (Tris), horseradish peroxidase (HRP),
ascorbate, phosphotungstic acid, poly-l-lysine solution (0.01%),
nerve growth factor-7S, and 3-(4,5-dimethyl-2-thiazolyl)-2,5-

Preparation of SiO2–cyclen nanochelator
SiO2 nanoparticles were synthesized by a modified literature
procedure. CTAB (0.5 g) was dispersed in water (200 mL)
with ultrasonic wave. Ammonium hydroxide (0.75 mL, 28 wt% NH3 in water) was then added to the solution with strong stir-
ing at room temperature, and TEOS (2.0 mL) was dropped in
slowly, giving rise to a white slurry. The resulting product was
centrifuged after 3 h, the CTAB was washed out by ethanol and
water, and SiO2 nanoparticles were obtained after drying at vacuum. SiO2–Cl nanoparticles were prepared according to the
modified literature procedure. SiO2 nanoparticles (200 mg)
were dispersed in isopropanol (200 mL) solution and were
allowed to react with 3-chloropropyltriethoxysilane (4.0 mL, in
excess) at 100 °C under nitrogen for 24 h. Excess 3-chloro-
opropyltriethoxysilane was removed by centrifugation and
redispersion in ethanol and water, followed by drying at room
temperature. Cyclen was tethered to the surface of SiO2–Cl nanoparticles according to the literature procedure. In a
typical reaction, cyclen (2.0 g, in excess) and 3-(4,5-dimethyl-2-thiazolyl)-2,5-

Chelation ability of SiO2–cyclen
SiO2–cyclen (6.0 mg) and SiO2–Cl (6.0 mg) nanoparticles were
dispersed into CuCl2 (1.0 mol L⁻¹, 2.0 mL, in excess) or Zn(Ac)2
(1.0 mol L⁻¹, 2.0 mL, in excess) solutions respectively, and
cultured at 37 °C for 3 h. The samples were cleaned by water to

Fig. 5 Neurotoxicity of Aβ40 in the absence or presence of metal ions
and chelators against PC12 cells after incubation at 37 °C for 48 h.
[Aβ40] = 10 μM, [Aβ40] : [M²⁺] : [chelator] = 1 : 2 : 2.
remove the excess CuCl₂ or Zn(Ac)₂, and digested by concentrated HNO₃ at 95 °C for 3 h. The amounts of chelated Cu²⁺ or Zn²⁺ in the SiO₂–cyclen nanochelators were determined by ICP-MS.

**BCA protein assay**

Aβ₄₀ (40 μM) in buffer solution (20 mM Tris–HCl/150 mM NaCl, pH 7.4, 197.6 μL) was incubated with or without Zn(Ac)₂ or CuCl₂ (80 μM) for 5 min at room temperature. Metal chelator (2.4 μL, 80 μM) was added to the solution and incubated at 37 °C for 24 h. The solution was centrifuged at 12 000 rpm for 30 min and each sample was transferred to individual wells of a flat-bottomed 96-well plate (Corning Costar Corp). The concentration of peptide in the supernatant was analyzed by the Micro BCA protein assay.

**ROS assay**

DCFH-DA stock solution (1 mM) as ROS probe was prepared in buffer (20 mM Tris–HCl/150 mM NaCl, pH 7.4). Horseradish peroxidase (HRP) stock solution (4 mg L⁻¹) was prepared with the same buffer. Sample solutions containing Aβ₄₀ (0.8 μM) and CuCl₂ (0.6 μM) were incubated with or without chelators (0.6 μM) at 37 °C for 20 h. Ascorbate (10 μM) was added to each sample and incubated at 37 °C for 1 h. The samples were transferred to individual wells of a flat-bottomed 96-well black plate. HRP (2 μL, 0.04 μM) and DCFH-DA (20 μL, 100 μM) were added to each solution and incubated for 10 min in the dark at room temperature. Fluorescence spectra (λₑₓ = 485 nm) in the range of 505–650 nm were measured by a Varioscan Flash microplate reader (Thermo Scientific).

**Morphology of Aβ aggregates**

Aβ₄₀ (20 μM) in buffer solution (20 mM Tris–HCl/150 mM NaCl, pH 7.4, 197.6 μL) was incubated with or without Zn(Ac)₂ or CuCl₂ (40 μM) for 5 min at room temperature. Metal chelator (2.4 μL, 40 μM) was added to the solution and incubated at 37 °C for 24 h. An aliquot of each solution (5 μL) was spotted onto carbon-coated copper grids for 30 min. The samples were stained with phosphotungstic acid [1.5% (w/v), pH 7.4]. The grids were blotted with filter paper to remove excess solution and air-dried before analysis on the TEM, operating with a voltage of 100 kV.

**Cell viability**

PC12 cells (American Type Culture Collection) were cultured in RPMI-1640 medium supplemented with 5% fetal bovine serum (FBS), antibiotics, and 10% horse serum in a 5% CO₂ humidified environment at 37 °C. The cells were plated at a density of 6000 cells per well on a poly-L-lysine-coated 96-well plates, and differentiated with 100 ng mL⁻¹ of nerve growth factor (NGF) in DMEM medium supplemented with 5% FBS at 37 °C with 5% CO₂ for 48 h. The cytotoxicity of Aβ₄₀ and Zn²⁺– or Cu²⁺–Aβ₄₀ with or without chelators toward the cells was measured after incubation for 48 h. The cells were treated with MTT (20 μL, 5 mg mL⁻¹ in PBS) for 4 h at 37 °C and lysed in DMSO for 30 min at room temperature in the dark. Absorbance values of formazan were determined by a Varioskan Flash microplate reader (Thermo Scientific) at 570 nm. The optical density (OD) was used to calculate the percentage of cell viability relative to the untreated control values, that is, (OD_sample – OD_blank)/(OD_control – OD_blank) × 100%, and the mean of three replicates was taken as the final result.

**In vivo BBB penetration assay**

C57BL/6j mice (8 week, male, 20 g, n = 12) were selected as animal models. SiO₂–cyclen nanochelators were injected intravenously (8 mg kg⁻¹ body weight) into the mice (3 mice in each group), and the brains of mice were acquired after 6 h, 12 h and 24 h, with mice without injection as controls. The brain samples were digested by concentrated HNO₃ at 95 °C, 30% H₂O₂ and concentrated HCl at 37 °C. The silicon amount in the samples was determined by ICP-MS. All experimental procedures are in accordance with the Guidelines for Care and Use of Laboratory Animals of Nanjing University, and experiments were approved by the Animal Ethics Committee of the Model Animal Research Center of Nanjing University.

**Conclusions**

In this study, a novel nanoscale chelator, SiO₂–cyclen, was reported, which is composed by cyclen as the metal-chelating unit and silica nanoparticle as a carrier of cyclen, for inhibiting the toxicity of Aβ aggregates. The results show that the SiO₂–cyclen nanochelator can effectively inhibit Aβ aggregation, reduce the generation of reactive oxygen species induced by the Cu–Aβ₄₀ complex, and protect cells from the metal-induced Aβ toxicity. Blood–brain barrier is a dynamic barrier protecting the brain against invading organisms and unwanted substances; it is also the most important barrier impeding the drug transport into the brain via the blood circulation. In vivo study demonstrated that the SiO₂–cyclen nanochelator can overcome the drawbacks of small chemicals (>400 Da) or peptides in passing across the BBB, which may have some reference value for the design of novel Aβ inhibitors.

**Conflicts of interest**

There are no conflicts to declare.

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