Published in final edited form as:

CNS Neurol Disord Drug Targets. 2012 February ; 11(1): 81–85.

Nanoparticle Delivery of Transition-Metal Chelators to the Brain: Oxidative Stress will Never See it Coming!

David J. Bonda¹, Gang Liu², Ping Men², George Perry^{1,3}, Mark A. Smith¹, and Xiongwei Zhu¹

¹Department of Pathology, Case Western Reserve University, Cleveland, Ohio 44106, USA

²Department of Radiology, University of Utah, Salt Lake City, Utah 84108, USA

³College of Sciences, University of Texas at San Antonio, San Antonio, Texas 78249, USA

Abstract

The pathological lesions typical of Alzheimer disease (AD) are sites of significant and abnormal metal accumulation. Metal chelation therapy, therefore, provides a very attractive therapeutic measure for the neuronal deterioration of AD, though its institution suffers fundamental deficiencies. Namely, chelating agents, which bind to and remove excess transition metals from the body, must penetrate the blood-brain barrier (BBB) to instill any real effect on the oxidative damages caused by the presence of the metals in the brain. Despite many advances in chelation administration, however, this vital requirement remains therapeutically out of reach: the most effective chelators—i.e., those that have high affinity and specificity for transition metals like iron and copper—are bulky and hydrophilic, making it difficult to reach their physiological place of action. Moreover, small, lipophilic chelators, which can pass through the brain's defensive wall, essentially suffer from their over-effectiveness. That is, they induce toxicity on proliferating cells by removing transition metals from vital RNA enzymes. Fortunately, research has provided a loophole. Nanoparticles, tiny, artificial or natural organic polymers, are capable of transporting metal chelating agents across the BBB regardless of their size and hydrophilicity. The compounds can thereby sufficiently ameliorate the oxidative toxicity of excess metals in an AD brain without inducing any such toxicity themselves. We here discuss the current status of nanoparticle delivery systems as they relate to AD chelation therapy and elaborate on their mechanism of action. An exciting future for AD treatment lies ahead.

Keywords

Alzheimer disease; amyloid-beta; chelator; nanoparticle; oxidative stress; transition-metal

Correspondence to: Xiongwei Zhu, Ph.D., Department of Pathology, Case Western Reserve University, 2103 Cornell Road, Cleveland, Ohio 44106 USA. Tel: 216-368-5903, Fax: 216-368-8964, xiongwei.zhu@case.edu. Gang Liu, Ph.D., Department of Radiology, University of Utah, 729 Arapleen Dr, Salt Lake City, Utah, 84108 USA. Tel: 801-581-3429, Fax: 801-581-7008, gang.liu@hsc.utah.edu.

Introduction

Alzheimer disease (AD) is a progressive and fatal neurodegenerative condition that afflicts millions of people around the world [1]. The deterioration of cognition and memory that characterizes AD has resisted efforts to develop an effective treatment, though much progress has been made in the last decade. However, current FDA-approved drugs, such as the cholinesterase inhibitors, are a far cry from a full cure: these agents merely attenuate symptoms of disease and, at best, only postpone the inevitable decline in general cognitive functions [2]. Consequently, the economic and societal burden of AD is increasing as the world's population ages. As an estimated 24 million people suffer from dementia worldwide [3], the associated health-care costs currently exceed \$100 billion per year [1, 4], and the emotional burden on the families of the afflicted is immeasurable. There is thus a clear need for an advanced therapeutic strategy for AD that can stop or even reverse its progression. The accumulation of metals such as iron and copper throughout the brain, and specifically within the pathological lesions of AD, provides an untapped target for disease treatment. While there exist many other opportunities for intervention throughout the course of the disease, metal chelation therapy is becoming increasingly attractive.

Oxidative Stress in AD

Although the etiology of AD is incompletely understood, oxidative stress resulting from a variety of intracellular malfunctions undoubtedly plays a key role [5]. There seems to exist a complex cascade whereby free-radical species, inevitably generated from the multitudes of redox reactions in metabolically hyperactive neurons [6], chemically alter vital macromolecules within the cell, such that significant damage is incurred [7–10]. Many in the field assert that it is the irreversible damage to neurons, brought about by this oxidative stress cascade, which elicits the infamous pathologies of AD (amyloid plaques and neurofibrillary tangles) and ultimately neuronal demise [11–13]. Indeed, the levels of oxidatively damaged mitochondrial DNA, proteins, and phospholipids in AD brains are elevated when compared to control cases [8–10]. Furthermore, these damages precede the appearance of the signature pathologies of AD that have long been held responsible for disease initiation [14–16]. It therefore seems likely that the most effective method of treatment of AD, one that would attenuate the root-cause disturbances, is one that targets oxidative stress.

Interestingly, the oxidative reactions in the brain can be catalyzed by transition metals, such as iron and copper [17, 18]. The likelihood that an oxidative reaction will take place in the brain is increased by regional concentrations of these metals, and in fact, some such transition metals, have been found in high concentrations in AD brains, accumulating specifically in the pathological lesions [19–23]. Additionally, amyloid- β (A β), a significant, though not causal, pathological factor in AD [24–26], may exert its toxicity through the formation of protease-resistant oligomeric and fibrillar forms of the peptide [27], which is also dependent upon transition-metals [28]. Therefore, metal chelating agents that selectively bind to, remove, and/or “redox-silence” transition metals provide excellent potential for therapeutic intervention in AD. Indeed, such chelators are becoming increasingly scrutinized for just such usage.

Metal Chelation Therapy for AD: Current Biochemical Shortcomings

Currently available metal-chelating compounds have been moderately successful in clinical trials for AD treatment [29]. Notably, while these agents have slowed the progression of AD in some cases [30, 31], they are severely limited in their effectiveness due to fundamental aspects of their biochemistry. The hexadentate iron chelator Desferrioxamine (DFO), for example, which tightly binds iron(III) and moderately binds aluminum, zinc, and copper (Figure 1A, B) [31–34], has impeded the progression of AD in clinical trials, despite its high molecular weight and hydrophilicity [35–37]. Its clearance of transition metals from the brain is the proposed mechanism for its effectiveness, and indeed, it is one of two iron chelators approved by the FDA for iron overload disease [29]. However, its bulky size and hydrophilicity, typical of hexadentate iron chelators (i.e., those that incorporate six atoms into the substrate-ligand bond to form the coordination complex (Figure 1B) [38] limit is capacity to penetrate the blood-brain barrier (BBB)—a vital requirement for any AD therapy. Rather, its success in clinical trials was the result of long, subcutaneous administrations of the compound [34, 39]; something quite impractical and unappealing for widespread AD treatment.

Smaller metal chelation compounds, on the other hand, typically have the ability to penetrate the BBB, but are toxic upon administration [37]. In particular, bi- or tri-dentate iron chelators (those that utilize two or three atoms in their substrate-ligand bonds, respectively), such as the α -ketohydroxypyridone derivatives, efficiently bind to and remove iron from intracellular pools; however, in doing so, they eliminate much of the supply of iron necessary for the functioning of human ribonucleotide reductase—a vital enzyme necessary for the reduction of ribonucleotides to deoxyribonucleotides, and thus for DNA synthesis and cell proliferation [37, 40–44]. Furthermore, due to their lipophilicity and small size, such compounds are also thought to penetrate the interior of the large ribonucleotide reductase complexes to chelate and remove the transition metal within them [45]. They thus both directly and indirectly inhibit the vital functioning of ribonucleotide reductase intracellularly and are toxic to proliferating cells. Notably, DFO and other hexadentate iron chelators are somewhat toxic as well, due to their removal of the iron involved in the redox cycling of these RNA enzymes; their toxicity, however, is much less than that of their lipophilic counterparts.

Ultimately, there exists a need to develop metal chelating agents that can effectively penetrate the BBB without inducing toxicity upon neurons. Fortunately, efforts are well underway in such a pursuit, and specifically, nanoparticle delivery of metal chelators has attracted much attention [28, 29]. Ideally, the nanoparticle delivery method will improve drug efficacy while reducing toxicity, thus providing a safe, non-invasive method of treatment.

Nanoparticle Delivery of Metal Chelation Compounds

Nanoparticle delivery systems provide an interesting and rather attractive approach to metal chelation therapy (Figure 2). These polymeric particles, ranging in size from ~10–1000 nm [46], are made from natural or artificial polymers [47], and are capable of binding to drug

compounds such that they may be delivered to physiological regions normally prohibitive of their entry. Indeed, nanoparticles present a method of entry into the BBB that AD pathologies will never see coming.

The method of BBB penetration that makes nanoparticle delivery of metal chelators so appealing is not fully known. However, there are a number of possibilities that likely work in combination to achieve the desired effect. These include [47]: i) increased retention of nanoparticles in blood-brain capillaries combined with absorption into capillary walls to create a higher concentration gradient, thus enhancing their transport across endothelial cell layers into the brain; ii) a surfactant effect that would lead to membrane fluidization and enhanced drug permeability; iii) an opening of tight junctions between endothelial cells; iv) endocytosis of the nanoparticle-chelator conjugate; v) transcytosis of said compound through the endothelial cell layer; and vi) an inhibition of the efflux system (i.e., P-glycoprotein) via polysorbate-80 (a nanoparticle coating proven to yield the most effective delivery of drugs across the BBB [48–50]). While each of these mechanisms is quite possible, the most probable one seems to be the endocytosis of the chelator-nanoparticle conjugate. Several studies confirm endocytosis of polysorbate-80 coated nanoparticles [49, 51–54]. Interestingly, absorption of apolipoprotein E (ApoE) on the surface of polysorbate-80 coated nanoparticles coincides with the latter's BBB penetration [49], providing key insights into the mechanism of action of the endocytosis. Specifically, it is possible that polysorbate-coated nanoparticles mimic low-density lipoprotein (LDL) absorption into the brain: as ApoE facilitates the delivery of LDL across the BBB [47], its absorption onto nanoparticle compounds may act via LDL-receptor-mediated endocytosis (Figure 3), thus granting hydrophilic chelators access to the brain.

Incidentally, this approach offers distinct advantages over other methods of chelator administration. First, the chelator needs not be lipophilic to enter the BBB, as the nanoparticle can carry across any compound to which it is covalently bound [29]. This directly eliminates much of the toxicity associated with the bi- or tri-dentate chelators that removed iron supplies from vital enzymes within the cell. Second, as noted above, nanoparticle delivery permits the use of hexadentate iron chelators that were previously too large and hydrophilic to penetrate the BBB [48, 50]. Third, iron-complexed chelators (i.e., those that have complexed with the transition metal within the brain) may be effectively removed from the brain via nanoparticles, thus completing the treatment regimen. As to the latter, it is equally necessary for a metal chelator to be able to exit the brain through the BBB as it is to enter it; a complexed chelator must therefore leave the brain after retaining its substrate. With lipophilic chelators, their removal from the brain becomes problematic once they have complexed with a transition metal, due to their resulting altered lipophilicity [29, 55]; they can no longer exit the BBB and themselves become progenitors of metal-associated oxidative damage [56, 57]. A nanoparticle delivery system, however, theoretically provides an adequate escape route for the chelator [29]. That is, the apolipoprotein system that the nanoparticle conjugates most likely mimic is also responsible for its removal from the brain [47, 57]. Consequently, the nanoparticle-chelator system would enable the full, desired effect of a metal chelator without any toxic side effect.

Recent evidence has confirmed the benefits of nanoparticle metal chelation. As stated above, a large body of literature suggests that the neurotoxicity of A β may result from the formation of protease-resistant oligomeric and fibrillar forms of the peptide [27], and that transition metals in the brain are partly responsible for their formation [28]. Correspondingly, reports on the effectiveness of nanoparticle delivery of transition metal chelators have demonstrated an effective prevention of A β aggregation and toxicity *in vitro*. In particular, a co-incubation of A β with chelator nanoparticle conjugates completely prevented A β precipitation *in vitro* under physiological conditions [28]. The cells were cultured with either A β , chelator nanoparticle conjugates, or both, and ultimately, the latter cases were significantly salvaged from A β -induced cell death. Importantly, the chelator-nanoparticle conjugates did not induce toxicity to neurons at the recorded concentrations, and cells treated with A β and the conjugates demonstrated similar rates of proliferation as the control cells. Indeed, nanoparticle delivery provided adequate protection of cortical neurons from A β -induced toxicity.

CONCLUSIONS

Ideally, nanoparticle chelator conjugate systems can be used to remove transition metals within the brain, prior to any clinical symptoms and possibly in prevention of disease onset. Although these chelators have been demonstrated to effectively stifle the effects of A β on cortical neurons in culture, such pathology is present in a brain well on its way through the disease course [2]. That is, as recent evidence suggests, A β is merely a secondary pathology of AD that is in fact secreted as a compensatory measure for the oxidative damages that an aging brain accumulates [2, 8–10]. Metal chelation therapies therefore have the potential to deter the formation of oxidative free radicals in the brain, if harnessed appropriately; such would ideally prevent the secretion and aggregation of hallmark AD pathologies that, once accumulated, incur severe damage upon surrounding neurons [58, 59].

Nanoparticle conjugation provides an exciting approach to chelator delivery. Conjugation maximizes effectiveness of metal chelator by granting large, hydrophilic compounds entry to the BBB [48–50]; reduces toxicity of chelation compounds by providing the complexed chelators an escape route [56, 57]; and increases chelator bioavailability [29], all while preserving the chelation capability of the compound [28]. A nanoparticle delivery system thus presents a therapeutic measure with a high potential for success in clinical AD cases; it will certainly yield beneficial results if instituted early enough. Further *in vivo* and *in vitro* analyses are warranted.

Acknowledgments

Work in the authors' laboratories is supported by the National Institutes of Health (R01 AG031852 to XWZ) and the Alzheimer's Association (IIRG-09-132087 to MAS).

References

1. Smith MA, Hirai K, Hsiao K, Pappolla MA, Harris PL, Siedlak SL, Tabaton M, Perry G. Amyloid-beta deposition in Alzheimer transgenic mice is associated with oxidative stress. *J Neurochem*. 1998; 70:2212–2215. [PubMed: 9572310]

2. Bonda DJ, Lee HP, Lee HG, Friedlich AL, Perry G, Zhu X, Smith MA. Novel therapeutics for Alzheimer's disease: an update. *Curr Opin Drug Discov Devel.* 2010; 13:235–246.
3. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M. Global prevalence of dementia: a Delphi consensus study. *Lancet.* 2005; 366:2112–2117. [PubMed: 16360788]
4. Marabini S, Matucci-Cerinic M, Geppetti P, Del Bianco E, Marchesoni A, Tosi S, Cagnoni M, Partsch G. Substance P and somatostatin levels in rheumatoid arthritis, osteoarthritis, and psoriatic arthritis synovial fluid. *Ann N Y Acad Sci.* 1991; 632:435–436. [PubMed: 1719897]
5. Smith MA, Sayre LM, Monnier VM, Perry G. Radical AGEing in Alzheimer's disease. *Trends Neurosci.* 1995; 18:172–176. [PubMed: 7778188]
6. Petersen RB, Nunomura A, Lee HG, Casadesus G, Perry G, Smith MA, Zhu X. Signal transduction cascades associated with oxidative stress in Alzheimer's disease. *J Alzheimers Dis.* 2007; 11:143–152. [PubMed: 17522439]
7. Bonda DJ, Wang X, Perry G, Smith MA, Zhu X. Mitochondrial dynamics in Alzheimer's disease: opportunities for future treatment strategies. *Drugs Aging.* 2010; 27:181–192. [PubMed: 20210366]
8. Zhu X, Castellani RJ, Takeda A, Nunomura A, Atwood CS, Perry G, Smith MA. Differential activation of neuronal ERK, JNK/SAPK and p38 in Alzheimer disease: the 'two hit' hypothesis. *Mech Ageing Dev.* 2001; 123:39–46. [PubMed: 11640950]
9. Zhu X, Lee HG, Perry G, Smith MA. Alzheimer disease, the two-hit hypothesis: an update. *Biochim Biophys Acta.* 2007; 1772:494–502. [PubMed: 17142016]
10. Zhu X, Raina AK, Perry G, Smith MA. Alzheimer's disease: the two-hit hypothesis. *Lancet Neurol.* 2004; 3:219–226. [PubMed: 15039034]
11. Castellani RJ, Harris PL, Sayre LM, Fujii J, Taniguchi N, Vitek MP, Founds H, Atwood CS, Perry G, Smith MA. Active glycation in neurofibrillary pathology of Alzheimer disease: N(epsilon)-(carboxymethyl) lysine and hexitol-lysine. *Free Radic Biol Med.* 2001; 31:175–180. [PubMed: 11440829]
12. Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, Jones PK, Ghanbari H, Wataya T, Shimohama S, Chiba S, Atwood CS, Petersen RB, Smith MA. Oxidative damage is the earliest event in Alzheimer disease. *J Neuropathol Exp Neurol.* 2001; 60:759–767. [PubMed: 11487050]
13. Su B, Wang X, Zheng L, Perry G, Smith MA, Zhu X. Abnormal mitochondrial dynamics and neurodegenerative diseases. *Biochim Biophys Acta.* 2010; 1802:135–142. [PubMed: 19799998]
14. Castellani RJ, Lee HG, Siedlak SL, Nunomura A, Hayashi T, Nakamura M, Zhu X, Perry G, Smith MA. Reexamining Alzheimer's disease: evidence for a protective role for amyloid-beta protein precursor and amyloid-beta. *J Alzheimers Dis.* 2009; 18:447–452. [PubMed: 19584435]
15. Lee HG, Casadesus G, Zhu X, Takeda A, Perry G, Smith MA. Challenging the amyloid cascade hypothesis: senile plaques and amyloid-beta as protective adaptations to Alzheimer disease. *Ann N Y Acad Sci.* 2004; 1019:1–4. [PubMed: 15246983]
16. Lee HG, Zhu X, Castellani RJ, Nunomura A, Perry G, Smith MA. Amyloid-beta in Alzheimer disease: the null versus the alternate hypotheses. *J Pharmacol Exp Ther.* 2007; 321:823–829. [PubMed: 17229880]
17. Halliwell, B.; Gutteridge, JMC. *Free Radicals in Biology and Medicine.* Oxford University Press; New York: 1999.
18. Olanow CW. An introduction to the free radical hypothesis in Parkinson's disease. *Ann Neurol.* 1992; 32(Suppl):S2–9. [PubMed: 1510376]
19. Kong S, Liochev S, Fridovich I. Aluminum(III) facilitates the oxidation of NADH by the superoxide anion. *Free Radic Biol Med.* 1992; 13:79–81. [PubMed: 1321073]
20. Lovell MA, Robertson JD, Teesdale WJ, Campbell JL, Markesbery WR. Copper, iron and zinc in Alzheimer's disease senile plaques. *J Neurol Sci.* 1998; 158:47–52. [PubMed: 9667777]
21. Sayre LM, Perry G, Harris PL, Liu Y, Schubert KA, Smith MA. In situ oxidative catalysis by neurofibrillary tangles and senile plaques in Alzheimer's disease: a central role for bound transition metals. *J Neurochem.* 2000; 74:270–279. [PubMed: 10617129]
22. Sayre LM, Perry G, Smith MA. Redox metals and neurodegenerative disease. *Curr Opin Chem Biol.* 1999; 3:220–225. [PubMed: 10226049]

23. Smith MA, Harris PL, Sayre LM, Perry G. Iron accumulation in Alzheimer disease is a source of redox-generated free radicals. *Proc Natl Acad Sci U S A*. 1997; 94:9866–9868. [PubMed: 9275217]
24. Hardy J. Alzheimer's disease: the amyloid cascade hypothesis: an update and reappraisal. *J Alzheimers Dis*. 2006; 9:151–153. [PubMed: 16914853]
25. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992; 256:184–185. [PubMed: 1566067]
26. Lee HG, Zhu X, Nunomura A, Perry G, Smith MA. Amyloid beta: the alternate hypothesis. *Curr Alzheimer Res*. 2006; 3:75–80. [PubMed: 16472207]
27. Selkoe DJ. The molecular pathology of Alzheimer's disease. *Neuron*. 1991; 6:487–498. [PubMed: 1673054]
28. Liu G, Men P, Perry G, Smith MA. Development of iron chelator-nanoparticle conjugates as potential therapeutic agents for Alzheimer disease. *Prog Brain Res*. 2009; 180:97–108. [PubMed: 20302830]
29. Liu G, Men P, Perry G, Smith MA. Nanoparticle and iron chelators as a potential novel Alzheimer therapy. *Methods Mol Biol*. 2010; 610:123–144. [PubMed: 20013176]
30. Kontoghiorghes GJ. New concepts of iron and aluminium chelation therapy with oral L1 (deferiprone) and other chelators. A review. *Analyst*. 1995; 120:845–851. [PubMed: 7741239]
31. McLachlan DR, Kruck TP, Lukiw WJ, Krishnan SS. Would decreased aluminum ingestion reduce the incidence of Alzheimer's disease? *CMAJ*. 1991; 145:793–804. [PubMed: 1822096]
32. Cuajungco MP, Faget KY, Huang X, Tanzi RE, Bush AI. Metal chelation as a potential therapy for Alzheimer's disease. *Ann N Y Acad Sci*. 2000; 920:292–304. [PubMed: 11193167]
33. Keberle H. The biochemistry of desferrioxamine and its relation to iron metabolism. *Ann N Y Acad Sci*. 1964; 119:758–768. [PubMed: 14219455]
34. Richardson DR, Ponka P. Development of iron chelators to treat iron overload disease and their use as experimental tools to probe intracellular iron metabolism. *Am J Hematol*. 1998; 58:299–305. [PubMed: 9692394]
35. Crowe A, Morgan EH. Effects of chelators on iron uptake and release by the brain in the rat. *Neurochem Res*. 1994; 19:71–76. [PubMed: 8139766]
36. Gassen M, Youdim MB. The potential role of iron chelators in the treatment of Parkinson's disease and related neurological disorders. *Pharmacol Toxicol*. 1997; 80:159–166. [PubMed: 9140134]
37. Hider RC, Porter JB, Singh S. The design of therapeutically useful iron chelators. In: Bergeron, RJ.; Brittenham, GM., editors. *The Development of Iron Chelators for Clinical Use*. CRC; Boca Raton: 1994. p. 353–371.
38. McNaught, AD.; Wilkinson, A. *IUPAC Compendium of Chemical Terminology*. Royal Society of Chemistry; Cambridge, UK: 1997.
39. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. *Blood*. 1997; 89:739–761. [PubMed: 9028304]
40. Cooper CE, Lynagh GR, Hoyes KP, Hider RC, Cammack R, Porter JB. The relationship of intracellular iron chelation to the inhibition and regeneration of human ribonucleotide reductase. *J Biol Chem*. 1996; 271:20291–20299. [PubMed: 8702762]
41. Hoyes KP, Hider RC, Porter JB. Cell cycle synchronization and growth inhibition by 3-hydroxypyridin-4-one iron chelators in leukemia cell lines. *Cancer Res*. 1992; 52:4591–4599. [PubMed: 1511427]
42. Lammers M, Follmann H. The ribonucleotide reductases -- A unique group of metalloenzymes essential for cell proliferation. *Struct Bonding*. 1983; 54:27–91.
43. Reichard P. Interactions between deoxyribonucleotide and DNA synthesis. *Annu Rev Biochem*. 1988; 57:349–374. [PubMed: 3052277]
44. Stubbe J. Ribonucleotide reductases: amazing and confusing. *J Biol Chem*. 1990; 265:5329–5332. [PubMed: 2180924]
45. Gerez C, Fontecave M. Reduction of the small subunit of Escherichia coli ribonucleotide reductase by hydrazines and hydroxylamines. *Biochemistry (Mosc)*. 1992; 31:780–786.

46. Kreuter J. Drug targeting with nanoparticles. *Eur J Drug Metab Pharmacokinet.* 1994; 19:253–256. [PubMed: 7867668]
47. Kreuter J. Nanoparticulate systems for brain delivery of drugs. *Advanced drug delivery reviews.* 2001; 47:65–81. [PubMed: 11251246]
48. Alyautdin RN, Tezikov EB, Ramge P, Kharkevich DA, Begley DJ, Kreuter J. Significant entry of tubocurarine into the brain of rats by adsorption to polysorbate 80-coated polybutylcyanoacrylate nanoparticles: an in situ brain perfusion study. *J Microencapsul.* 1998; 15:67–74. [PubMed: 9463808]
49. Kreuter J, Shamenkov D, Petrov V, Ramge P, Cychutek K, Koch-Brandt C, Alyautdin R. Apolipoprotein-mediated transport of nanoparticle-bound drugs across the blood-brain barrier. *J Drug Target.* 2002; 10:317–325. [PubMed: 12164380]
50. Schroeder U, Sommerfeld P, Ulrich S, Sabel BA. Nanoparticle technology for delivery of drugs across the blood-brain barrier. *J Pharm Sci.* 1998; 87:1305–1307. [PubMed: 9811481]
51. Alyautdin RN, Reichel A, Lobenberg R, Ramge P, Kreuter J, Begley DJ. Interaction of poly(butylcyanoacrylate) nanoparticles with the blood-brain barrier in vivo and in vitro. *J Drug Target.* 2001; 9:209–221. [PubMed: 11697206]
52. Borchard G, Audus KL, Shi F, Kreuter J. Uptake of surfactant-coated poly(methyl methacrylate)-nanoparticles by bovine brain microvessel endothelial cell monolayers. *Int J Pharm.* 1994; 110:29–35.
53. Kreuter J, Alyautdin RN, Kharkevich DA, Ivanov AA. Passage of peptides through the blood-brain barrier with colloidal polymer particles (nanoparticles). *Brain Res.* 1995; 674:171–174. [PubMed: 7773690]
54. Ramge P, Unger RE, Oltrogge JB, Zenker D, Begley D, Kreuter J, Von Briesen H. Polysorbate-80 coating enhances uptake of polybutylcyanoacrylate (PBCA)-nanoparticles by human and bovine primary brain capillary endothelial cells. *Eur J Neurosci.* 2000; 12:1931–1940. [PubMed: 10886334]
55. Porter JB, Gyparaki M, Burke LC, Huehns ER, Sarpong P, Saez V, Hider RC. Iron mobilization from hepatocyte monolayer cultures by chelators: the importance of membrane permeability and the iron-binding constant. *Blood.* 1988; 72:1497–1503. [PubMed: 3179437]
56. Liu G, Garrett MR, Men P, Zhu X, Perry G, Smith MA. Nanoparticle and other metal chelation therapeutics in Alzheimer disease. *Biochim Biophys Acta.* 2005; 1741:246–252. [PubMed: 16051470]
57. Liu G, Men P, Harris PL, Rolston RK, Perry G, Smith MA. Nanoparticle iron chelators: a new therapeutic approach in Alzheimer disease and other neurologic disorders associated with trace metal imbalance. *Neurosci Lett.* 2006; 406:189–193. [PubMed: 16919875]
58. Rottkamp CA, Raina AK, Zhu X, Gaier E, Bush AI, Atwood CS, Chevion M, Perry G, Smith MA. Redox-active iron mediates amyloid-beta toxicity. *Free Radic Biol Med.* 2001; 30:447–450. [PubMed: 11182300]
59. Smith MA, Zhu X, Tabaton M, Liu G, McKeel DW Jr, Cohen ML, Wang X, Siedlak SL, Dwyer BE, Hayashi T, Nakamura M, Nunomura A, Perry G. Increased iron and free radical generation in preclinical Alzheimer disease and mild cognitive impairment. *J Alzheimers Dis.* 2010; 19:363–372. [PubMed: 20061651]

A

B

Figure 1.

The hexadentate metal chelator Desferrioxamine (DFO) in its isolated (A) and complexed (B) forms.

Figure 2.

The hexadentate chelator DFO conjugated to a nanoparticle (shown here) has the potential to enable the hydrophilic molecule's passage across the blood-brain barrier.

Figure 3.

The proposed method of nanoparticle-chelator conjugate entry across BBB. Upon absorption of APOE lipoprotein to the surface of the Polysorbate-80 coated nanoparticle conjugate (1), the particle mimics LDL and binds to LDL-receptor (2) stimulating LDL-mediated endocytosis (3,4).