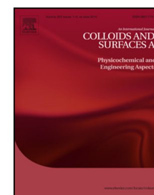
Colloids and Surfaces A: Physicochem. Eng. Aspects 442 (2014) 157–163

Contents lists available at ScienceDirect

Colloids and Surfaces A: Physicochemical and Engineering Aspects

journal homepage: www.elsevier.com/locate/colsurfa



Tunable plasma lipoprotein uptake/transport across the blood–brain barrier☆

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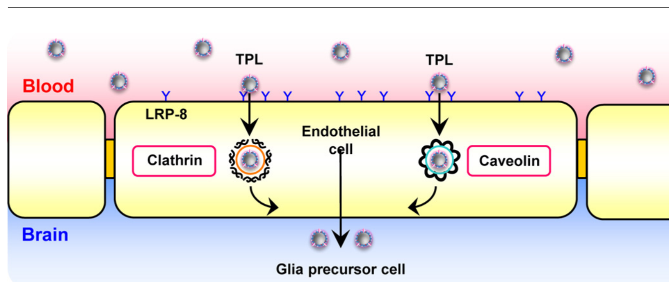
HIGHLIGHTS

- Biotechnological tools such as biocompatible nanoparticles have promising potential for theranostic strategies.
- Our study demonstrates the application of specifically constructed nanoparticles in the form of tunable plasma lipoproteins.
- Tuning of phosphatidylcholines and apolipoprotein B100 on nanoparticle surfaces is especially helpful for delivery route of glial precursor cells.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 30 November 2012
Received in revised form 19 April 2013
Accepted 15 May 2013
Available online 29 May 2013

Keywords:
Apolipoprotein B100
Nanoparticle
Glia
Blood–brain barrier
Surfactant
Lipoprotein

ABSTRACT

Brain development and maintenance requires transportation of cerebral sustenance across the blood–brain barrier. Disorders of this process can induce neurodegenerative diseases, which can affect numerous patients and incur significant treatment expenses. Recent scientific advances suggest that knowledge of this transportation will lead to the development of tailor-made theranostic strategies. Biotechnological tools such as biocompatible nanoparticles have promising potential in this context, however, information about their consequences in the brain is largely unknown. The present study demonstrates the application of specifically constructed cerebral sustenance nanoparticles in the form of tunable plasma lipoproteins to provide information about their pathways to the brain and delivery to glia cells. Individual cell analysis in brain sections enabled us to understand the accumulation of tunable plasma lipoproteins in the cerebral cortex, striatum, and cerebellum, which have been previously identified as the incident regions of Alzheimer's disease, Parkinson's disease, and spinocerebellar ataxia. The adjustability of the tunable plasma lipoproteins enables their use in theranostic applications against neurodegenerative diseases.

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http://dx.doi.org/10.1016/j.colsurfa.2013.05.053

1. Introduction

The brain regulates mental and motor functions, which are based on neural networks. Neural network changes such as synaptogenesis, myelination, and neuro- and glio-genesis are associated with environmental factors and individual life events [1]. These changes are produced and preserved by cerebral sustenance transportation across the blood-brain barrier (BBB) [2]. It is generally known that glial cells such as astrocytes and oligodendrocytes play roles in brain development and maintenance [3]. They are not only relevant to the functions of synaptogenesis, myelination, and BBB, but are also involved in the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), and progressive spinocerebellar ataxia (SCA) [2,3]. In addition, it suggests that AD, PD, and SCA generation are induced by the loss of synapses and myelin or the malfunction of BBB in the brain [2,3]. Glial cells are responsible for the preservation of synapses, myelin, and BBB [2,3]. Therefore, innovation to achieve the aim of delivering drugs to glial cells will lead to key advancements in the development of effective theranostic methods [3,4]. However, the pathway from the plasma to glial cells for delivering drugs is as yet unknown.

Neurodegenerative diseases (NDs) such as AD, PD, and SCA are strongly associated with brain aging. These pathological phenotypes have been found in specific brain regions such as the cerebral cortex (AD), striatum (PD), and cerebellum (SCA) [5,6]. Clinical studies suggest that low vitamin A, D, and E levels in plasma contribute to AD, PD and SCA pathogenesis [5,6]. Since mammals are not able to synthesize essential substances such as fat-soluble vitamin A, D, and E, they must be extracted from their diet in the form of plant carotenes or animal retinyl esters, which are stored as retinoids in the liver following ingestion. These vitamins are subsequently transported by plasma lipoproteins (PLs) from the liver into the cardiovascular system [7,8]. But, incorporation of vitamin A, D, and E into PLs through retinol-binding proteins, vitamin D-binding proteins, and α-tocopherol transfer proteins are impaired in AD, PD, and SCA [5,6]. Moreover, it is widely accepted that vitamin A, D, and E are required for synaptogenesis, myelination, and glio-differentiation [9]. Consequently PLs that carry vitamins across the BBB could be vital for glial cells such as astrocytes and oligodendrocytes.

PL core consists mainly of triglycerides, (esterified) cholesterols, fat-soluble vitamins, fatty acids, and hormones, while the shell is composed of phospholipids, primarily phosphatidylcholines (PCs) and sphingomyelins, and apolipoproteins (Apos), such as Apo-A1-4, Apo-B48, Apo-B100, Apo-C1-3, ApoD, Apo-E2-4, and Apo-J [7,8]. PLs in plasma are found in high-density lipoproteins (HDLs), low-density lipoproteins (LDLs), intermediate-density lipoproteins (IDLs), very low-density lipoproteins (VLDLs), and chylomicrons. LDLs, IDLs, and VLDLs, which carry fat-soluble vitamins, mainly contain Apo-B100 [7,8]. Here, we hypothesize that PCs and Apo-B100 in LDLs would be targetor for glial cells. There is now evidence that glial cells highly express heparan sulfate proteoglycans and chondroitin sulfate proteoglycans, which can bind to LDLs [10,11]. Unfortunately, LDL pathway to glial cells has yet been uncharacterized.

In previous studies of brain delivery system, it has been shown that the modifications of nanoparticle surfaces are common approach to achieve novel drug therapies for delivering nanoparticles to the brain [12–15]. Actually, polysorbate 80 with Apo-B or Apo-E-mediated transport at the BBB has been demonstrated as targets for nanoparticle delivery to the brain [12]. However, it has been suggested that the polysorbate 80 induce toxic affects on the BBB permeability [12]. Therefore, future study for novel modification of nanoparticle surfaces should be focus on. Moreover, gold nanoparticles (AuNPs) are useful for the development of clinical applications and treatment strategies, since AuNPs are intended for practical use as contrast agents for an X-ray computed tomography (CT) [16–18].

Here our study demonstrates the application of specifically constructed cerebral sustenance nanoparticles in the form of tunable plasma lipoproteins (TPLs) in order to brain delivery system specifically targeting a subpopulation of glial cells.

2. Materials and methods

2.1. Preparation and characterization of tunable plasma lipoproteins

AuNPs of 20 nm diameter were produced by the Turkevich method [19] and were diluted to a final concentration of 500 μg/ml. PCs (850325P, Avanti Polar Lipids, USA) were dissolved by vortexing in distilled water (ppb level) to a concentration of 1 mg/ml at 37 °C. Aggregates were removed by filtration through a 100 nm cutoff filter (SLVV033RS, Millipore, USA). A 400 μl aliquot of the resulting solution was added to 100 μl of the AuNPs. The AuNPs were coated with the PCs by stirring overnight at 37 °C. The sizes and shapes of the resulting TPLs were determined via transmission electron microscopy (TEM) (JEM-1200 EXII, JEOL, Japan) with negative staining with uranyl acetates. The cell tracker, CM-DiI (DiI) (C7000, Molecular Probes™, USA), was added at a rate of 0.5 μl per 500 μl of distilled water from a 1 mg/ml stock solution in DMSO. Next, 500 μl of the diluted DiI-solution was mixed with 500 μl of the PC-coated AuNPs by gentle stirring, followed by incubation at 37 °C for 30 min inside a sealed tube. Finally, 1 ml of 1 μg/ml Apo-B100 (A5353, Sigma, USA) in saline was added to 1 ml of the DiI-labeled PC-coated AuNPs and incubated for 3 h at 37 °C. The TPLs were re-dispersed in saline and residual PC, Apo, and DMSO solvent were removed by centrifuging twice at 20,000 × *g* for 5 min. Remaining aggregates were removed by filtration using a 100 nm cutoff filter. Both their hydrodynamic diameter and their PDI were determined by DLS measurements (Nano-ZS, Sysmex, Netherlands). Particle number data (%) were obtained from distribution analyses of the non-negative linear least squares method.

2.2. In vitro experiments

Endothelial cells (ECs) (bEnd.3, ATCC, USA) from mouse brains were cultured in cell culture medium (DMEM, Wako, Japan), supplemented with 10% heat-inactivated fetal bovine serum (Bio West, France) and 0.1% gentamycin (Sigma–Aldrich, USA). Incubation was carried out at 37 °C in a humidified atmosphere of 5% CO_2. The ECs were seeded to a density of 0.7×10^4 cells/cm^2 onto glass plates (1.1 cm^2) that were coated with rat-tail collagen to a density of 5 μg/cm^2 inside flat bottom 24-well plates (area: 1.55 × 1.55 cm^2, height: 1.75 cm). ECs that grew to sub-confluence, corresponding to final cell densities of 2.5×10^4 cells/cm^2, were treated with TPL for different incubation times (6 and 12 h). 100 μl of TPL were added to 900 μl of the cell medium to achieve a final concentration of 2.5 μg/ml. The TPL-containing cell culture medium was replaced with non-TPL-enriched cell medium 30 min after the end of the 12 h incubation. The ECs were then washed twice with PBS and fixed with 4% paraformaldehyde. For the immunocytochemical analyses, ECs were blocked with 3% goat serum for 20 min and were incubated overnight with primary antibodies to clathrin HC H-300 (sc-9069, Santa Cruz Biotechnology, USA), caveolin-1 (C-term), LRP8, and LDL receptor (C-term) (1249-1, 3156-1, and 1956-1, Epitomics Inc., USA) at 4 °C. They were subsequently incubated with secondary antibodies: Alexa Fluor®

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