Journal of Controlled Release 261 (2017) 43–61

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Review article

Self-assembled amphiphilic core-shell nanocarriers in line with the modern strategies for brain delivery

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ARTICLE INFO

Keywords:
Brain targeting
Core-shell nanocarriers
Micelles
Nanotechnology

ABSTRACT

Disorders of the central nervous system (CNS) represent increasing social and economic problems all over the world which makes the effective transport of drugs to the brain a crucial need. In the last decade, many strategies were introduced to deliver drugs to the brain trying to overcome the challenge of the blood brain barrier (BBB) using both invasive and non-invasive methods. Non-invasive strategy represented in the application of nanocarriers became very common. One of the most hopeful nanoscopic carriers for brain delivery is core-shell nanocarriers or polymeric micelles (PMs). They are more advantageous than other nanocarriers. They offer small size, ease of preparation, ease of sterilization and the possibility of surface modification with various ligands.

Abbreviations: 17-AAG, 17-Allylamino-17-demethoxy geldanamycin; 5-FU, 5-flourouracil; AAV, adeno-associated virus; ABC, ATP binding cassette; Ach, acetyl choline; AFM, atomic force microscopy; AmB, amphotericin B; AMT, adsorbtive-mediated transcytosis; APN, aminopeptidase N; Apo, apolipoprotein; ATRA, all-trans retinoic acid; BBB, blood brain barrier; BCECs, brain capillary endothelial cells; BCNU, bis-chloroethylnitrosourea; BCSFB, blood–cerebrospinal fluid barrier; BMECs, brain microvascular endothelial cells; BS, bile salt; BVECs, brain vascular endothelial cells; CA_8, dendritic octamer of cholic acid; CAC, critical aggregation concentration; CD, choline derivatives; CDs, cyclodextrins; cl-micelles, cross linked micelles; CIMS, core-inversible micelles; CMC, critical micelle concentration; CMT, carrier-mediated transport; CNS, central nervous system; CPPs, cell penetrating peptides; CPT, captothecin; cRAD, cyclic-arginine-alanine-aspartic acid; CREKA, cysteine-arginine-glutamic acid-lysine-alanine; cRGD, cyclic Arginine-Glycine-Aspartic acid; CRM, cross reacting material; CSF, cerebrospinal fluid; CS-SA, stearic acid-grafted chitosan; CT, X-ray computed tomography; DACHPt, (1,2-diaminocyclohexane) platinum(II); DHA, dehydroascorbic acid; DiR, near-infrared fluorescent dye; DL, drug loading; DLS, dynamic light scattering; DOM, domperidone; DOPE, dioleolyphosphatidyl ethanolamine; DOX, doxycycline; DPA, 3,30-dithiodipropionic acid; DPc, dendrimerphthalocyanine; DSPE, distearoylphophatidyl ethanolamine; DSPE-PEG, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-methoxy(polyethylene glycol); DT, diphtheria toxin; DTR, diphtheria toxin receptor; DTSSP, 3,3′-dithiobis(sulfosuccinimidylpropionate); DTX, docetaxel; ED, 1,2-ethylenediamine; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride; EE, encapsulation efficiency; EPR, enhanced permeability and retention effect; FA, folic acid; GBM, glioblastoma multiforme; GLUT, glucose transporter; GLUT-1 scFv, GLUT1 antibody single chain fragment variable; GTA, glycidyltrimethylammonium chloride; HIV, human immunodeficiency virus; HRP, horseradish peroxidase; HSA, human serum albumin; HSVtk, herpes simplex virus thymidine kinase gene; IAs, inhaled anaesthetics; ITZ, itraconazole; LAT1, large neutral amino-acid transporter type 1; LCST, lower critical solution temperature; LINCL, late infantile neuronal ceroidlipofuscinosis; LRP, lipoprotein receptor-related protein; Lt, lactoferrin; LTG, lamotrigine; LtR, lactoferrin receptor; mAbs, monoclonal antibodies; Mal, maliemide; MAN, aminophenyl-α-d-mannopyranoside; mPEG-*b*-P(Glu), poly(ethyleneglycol)-*b*-poly(L-glutamic acid); mPEG-*b*-PCL-*b*-PPEEA, monomethoxy poly(ethylene glycol)-*block*-poly(ε-caprolactone)-*block*-poly(2-aminoethyl ethylene phosphate); mPEG-OA, monomethoxy poly(ethylene glycol)-oleate; mPEG-PAHy-GTA, methoxy poly(ethylene glycol)-α,β-polyasparthydrazide-glycidyltrimethylammonium; m-PEG-PDMAEMA, methoxy poly(ethylene glycol)-poly(2-(dimethylamino)ethyl methacrylate; mPEG-St, mPEGylated starch; MRI, magnetic resonance imaging; MRP, multidrug resistant protein; MRSA, methicillin-resistant *Staphylococcus aureus*; NGR, Asn-Gly-Arg peptide; NHS, *n*-hydroxysuccinimidyl; NIR, near-infrared; NPs, nanoparticles; OX26, an anti-TfR antibody; PC, phosphatidylcholine; PCL-*b*-p(NIPAAm-*co*-DMA), poly(ε-caprolactone)-*block*-poly(*N*-isopropylacrylamide-*co*-*N*,*N*-dimethylacrylamide); PCL-PEEP, poly(ε-caprolactone)-*block*-poly(ethyl ethylene phosphate); PDI, polydispersity index; PEG, poly(ethylene glycol); PEG-*b*-Chol, poly(ethylene glycol)-*block*-cholesterol; PEG-*b*-P(NIPAAm-*co*-NHPAAm), poly(ethylene glycol)-*block*-poly(*N*-isopropylacrylamide-*co*-*N*-(4-hydroxyphenethyl)acrylamide); PEG-*b*-PCL, poly(ethylene glycol)-*block*-poly(ε-caprolactone); PEG-*b*-PLA, poly(ethylene glycol)-*block*-poly(lactic acid); PEG-*b*-PLL, poly(ethylene glycol)-*block*-poly(L-lysine); PEG-*b*-PMA, poly(ethylene glycol)-*block*-poly(methacrylic acid); PEG-PAE-API, poly(ethylene glycol)-poly(*b*-amino ester)-1-(3-aminopropyl) imidazole; PEG-PBLA, poly(ethylene glycol)-poly(*b*-benzyl-L-aspartate; PEG–PGlu–PPhe, poly(ethylene glycol)-poly(glutamic acid)-poly(phenylalanine); PEG-pLys-pPhe, poly(ethylene glycol)-*b*-poly(L-lysine)-*b*-poly(L-phenylalanine); PE-mPEG, 1,2 distearoyl-snglycero-3-phosphoethanolamine-*N*-(methoxy(polyethylene glycol)); PEO, polyethylene oxide; P-gp, P-glycoprotein; PHEA-EDA-PLA, α,β-poly((*N*-hydroxyethyl)-DL-aspartamide)-ethylenediamine-poly(lactic acid); pHPMA-*co*-pLMA, poly(*N*-(2-hydroxypropyl)-methacrylamide)-poly(lauryl methacrylate); PIC, polyion complex; PLA-*b*-PDMAEMA, poly(lactic acid)-poly(dimethylaminoethyl methacrylate; PMs, polymeric micelles; pNIPAAm, poly(*N*-isopropyl acrylamide); PPO, polypropylene oxide; PS_{80}, polysorbate 80; PTX, paclitaxel; R3V6, 3-arginine and 6-valine; R7L10, 7-arginine and 10-leucine; RAFT, reversible addition-fragmentation chain transfer; RES, reticuloendothelial system; RMT, receptor-mediated transcytosis; ROP, metal-free organo catalyticpolymerization; RT, radiation therapy; RVG, rabies virus glycoprotein; SACDs, sodium alginate cholesterol derivatives; SA-g-pNIPAAm, sodium alginate-*graft*-poly(*N*-isopropylacrylamide); SAH, subarachnoid hemorrhage; SDS, sodium dodecyl sulphate; siRNA, small interfering RNA; SMA, poly(styrene-*co*-maleic anhydride); SPIONs, superparamagnetic iron oxide nanoparticles; sPMI, stapled peptide antagonist of both MDM2 and MDMX; T7, His-Ala-Ile-Tyr-Pro-Arg-His peptide; Tat, trans-activating transcriptional activator; Td, tryptophan derivative; TEER, transendothelial electrical resistance; TEM, transmission electron microscope; Tf, transferrin; TFF3, trefoil factor 3; TfR, transferrin receptor; TGN, TGNYKALHPHNG peptide; Tjs, tight junctions; TMZ, temozolomide; TPGS, D-alphatocopheryl polyethylene glycol succinate; UV, ultra-violet; VEGF-siRNA, vascular endothelial growth factor-small interfering RNA; YC1, 5α-cholestane-24-methylene-3β,5α,6β,19-tetraol; Zot, zonulaoccludens toxin

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http://dx.doi.org/10.1016/j.jconrel.2017.06.019
Received 17 March 2017; Received in revised form 16 June 2017; Accepted 20 June 2017
Available online 23 June 2017

Hence, the aim of this review is to discuss modern strategies for brain delivery, micelles as a successful delivery system for the brain and how micelles could be modified to act as “magic bullets” for brain delivery.

1. Introduction

Diseases can affect both brain and spinal cord causing central nervous system (CNS) neurological or psychiatric disorders. CNS diseases are numerous and can be classified under three categories [1,2]. The first category includes neurological infectious diseases caused by bacteria, viruses and fungi such as meningitis, encephalitis, Lyme encephalopathy, Creutzfeld–Jakob and cerebral toxoplasmosis. The second category includes neurological disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, seizures, dementia, depression, multiple sclerosis, mononeuropathy and polyneuropathy. The last category involves brain tumors and physical injuries such as cerebral tumors, thrombosis, embolism, hemorrhage and vasculitis. CNS disorders represent an increasing problem both socially and economically all over the word with regard to both the number of patients and the cost of therapy.

So far the CNS disorders are responsible for almost 11% of disease burden - as they affect 1.5 billion people - and about 1% of deaths worldwide [3]. Hence, efficient treatment of CNS diseases became a crucial issue. Despite the presence of relatively high blood flow to the CNS (total surface area of 20 m^2 and a total length of 400 miles), the effective targeting presents a great problem [4].

The two main barriers hinder the brain delivery are the blood–brain barrier (BBB) and the blood–cerebrospinal fluid barrier (BCSFB), with the first one regarded as the most important obstacle to the brain parenchyma [5–7]. Generally, invasive strategies were oftenly used [7]. Lately, non-invasive strategies involving nanocarriers delivery became the most targeted strategy [8]. Polymeric micelles (PMs) as self-assembled amphiphilic core-shell nanocarriers are among the promising nanoscopic carriers [9,10]. During the last decade, numerous studies utilized PMs as an efficient drug delivery system for brain delivery [11–13]. In this review, we will highlight the modern strategies for brain delivery. Likewise, an in-depth focus on PMs as promising nanocarriers for brain targeting will be upraised. The review will emphasize at the end the use of PMs as “magic bullets” in brain therapeutics.

2. Challenge of the BBB

Being of selective nature, BBB offers to the brain protective functions against noxious circulating substances, while at the same time affording needed nutrients for an adequate brain function [5]. It is physiologically made up of three layers; the first is the inner endothelial cell layer forming the capillary wall and containing tight junctions (Tjs); the second is the basement membrane and finally the third layer composed of pericytes and astrocytic feet processes lying on the basement membrane [2] (Fig. 1). These whole anatomical and physiological properties generate the concept of BBB.

Tjs, acting as *a physical barrier*, are formed and regulated by claudins (e.g. claudins 1 and 5), occluding, annexin-1 and junction adhesives, which are protein molecules linked together by zonulaoccludens and cingulin to the beta-actin cytoskeleton. They are filling the gap within brain vascular endothelial cells creating the tight junctions. This will not only reduce the paracellular movement of substances, but also will contribute to the high transendothelial electrical resistance (TEER) of $> 1500\ \Omega\ cm^2$ [2,8].

Astrocytes and pericytes play essential role in maintaining BBB function in healthy CNS and following injuries. Astrocytes main roles are in the healthy CNS and include blood flow regulation, nutrients provision and assistance of extracellular ion balance. Moreover, following traumatic injuries, it has a fundamental effect on the reformation of the damaged brain and spinal cord [5,14]. Pericytes, responsible for growth factors secretion or changes in the extracellular matrix, are important in the maturation, renovation and conservation of the vascular system. Besides, their participation in molecules delivery across the BBB and vascular permeability control is well defined [5,15].

The concept of *biochemical barrier* is established from the occupancy of many receptors, transporter proteins and efflux pumps that permit the passage of certain vital substances into the brain and prevent the others [17]. Actually, during physiological and pathological processes, BBB is included in several functions like tissue homeostasis, fibrinolysis and coagulation, adjustment of vascular tone, blood cell movement and activation, preservation of neuronal environment and vascularization of normal neoplastic tissues [5].

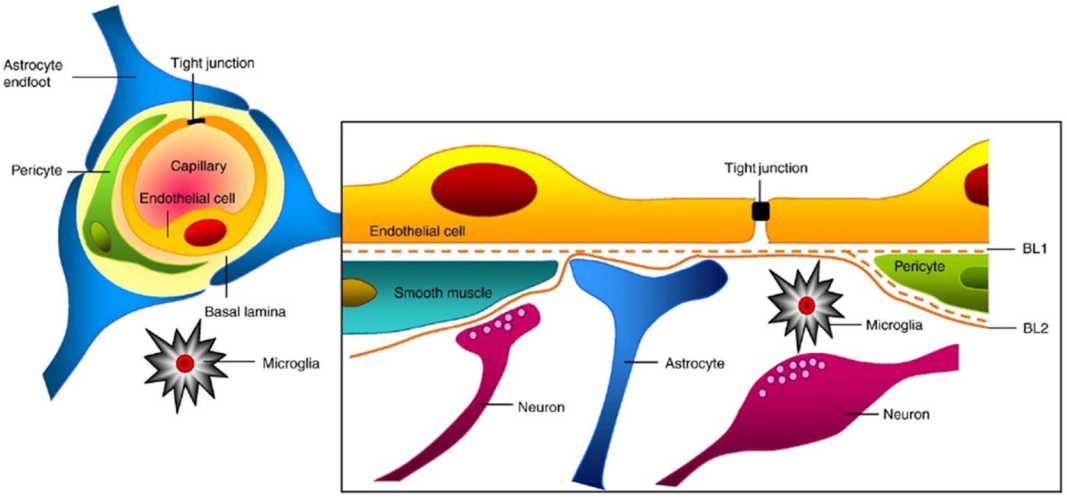

Fig. 1. Schematic illustration of blood brain barrier.
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