Journal of Controlled Release 190 (2014) 637–663

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Review

Agile delivery of protein therapeutics to CNS

Xiang Yi [a,*], Devika S. Manickam [a], Anna Brynskikh [b], Alexander V. Kabanov [a,c,*]

[a] Division of Molecular Pharmaceutics and Center for Nanotechnology in Drug Delivery, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
[b] Department of Pharmaceutical Sciences and Center for Drug Delivery and Nanomedicine, University of Nebraska Medical Center, Omaha, NE 68198, USA
[c] Faculty of Chemistry, M.V. Lomonosov Moscow State University, 119899 Moscow, Russia

ARTICLE INFO

Article history:
Received 21 April 2014
Accepted 13 June 2014
Available online 21 June 2014

Keywords:
Protein therapeutics
Central nervous system
Blood–brain barrier
Protein delivery
Administration route
Brain delivery

ABSTRACT

A variety of therapeutic proteins have shown potential to treat central nervous system (CNS) disorders. Challenge to deliver these protein molecules to the brain is well known. Proteins administered through parenteral routes are often excluded from the brain because of their poor bioavailability and the existence of the blood–brain barrier (BBB). Barriers also exist to proteins administered through non-parenteral routes that bypass the BBB. Several strategies have shown promise in delivering proteins to the brain. This review, *first*, describes the physiology and pathology of the BBB that underscore the rationale and needs of each strategy to be applied. *Second*, major classes of protein therapeutics along with some key factors that affect their delivery outcomes are presented. *Third*, different routes of protein administration (parenteral, central intracerebroventricular and intraparenchymal, intranasal and intrathecal) are discussed along with key barriers to CNS delivery associated with each route. *Finally*, current delivery strategies involving chemical modification of proteins and use of particle-based carriers are overviewed using examples from literature and our own work. Whereas most of these studies are in the early stage, some provide proof of mechanism of increased protein delivery to the brain in relevant models of CNS diseases, while in few cases proof of concept had been attained in clinical studies. This review will be useful to broad audience of students, academicians and industry professionals who consider critical issues of protein delivery to the brain and aim developing and studying effective brain delivery systems for protein therapeutics.

Contents

Abbreviations: Aβ, amyloid β; Ab-InsR, antibodies against insulin receptor; Ab-TfR, antibodies against transferrin receptor; AD, Alzheimer's disease; Aerosol OT, bis-(2-ethylhexyl) sulfosucciate; ALS, amyotrophic lateral sclerosis; ApoB, apolipoprotein B; ApoE, apolipoprotein E; ASA, arylsulfatase A; AUC, area under the curve; α2-GP, α2-glycoprotein; Ab-BACE1, antibodies against β-secretase; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; BIC, block ionomer complexes; BChE, butyrylcholinesterase; bFGF, basic fibroblast growth factor; BMECs, brain microvessel endothelial cells; BMM, bone-marrow derived macrophages; CED, convection-enhanced delivery; Chol, cholesterol; CMC, critical micelle concentration; CNS, central nervous system; CPPs, cell-penetrating peptides; CSF, cerebrospinal fluid; DIO, diet-induced obese; DOPE, dioleoyl phosphatidylethanolamine; DPP-IV, dipeptidyl peptidase IV; EPO, erythropoietin; GDNF, glial cell-derived neurotrophic factor; GFAP, gliofibrillar acid protein; GLP-1, glucagon-like peptide 1; GSH, reduced glutathione; EAE, experimental autoimmune encephalomyelitis; ECS, extracellular space; EGF, epidermal growth factor; EGFR, EGF receptor; ERT, enzyme replacement therapy; FDA, Food and Drug Administration; FGF, fibroblast growth factor; HAD, HIV-1-associated dementia; HIV-1, human immunodeficiency virus 1; HRP, horseradish peroxidase; HPMA, N-(2-hydroxypropyl)-methacrylamide; I2S, iduronate-2-sulfatase; INB, intranasal-to-brain; i.c.v., intracerebroventricular; IGF-I, insulin-like growth factor I; i.m., intramuscular; i.n., intranasal; i.t., intrathecal; InsR, insulin receptor; i.v., intravenous; KLH, keyhole limpet hemocyanin; LDL, low-density lipoprotein; LRP1, ligand of LDL receptor-related protein 1; LRP2, LRP1, ligand of LDL receptor-related protein 2; LSDs, lysosomal storage disorders; M6P, mannose 6-phosphate; MCAO, middle cerebral artery occlusion model; MPS I, mucopolysaccharidosis I; MPS II, mucopolysaccharidosis II; MS, multiple sclerosis; NGF, nerve growth factor; NT-3, neurotrophin-3; MTf, melanotransferrin; NVU, neurovascular unit; OXM, oxyntomodulin; PACAP, pituitary adenylate cyclase activating polypeptide; PBCA, poly(butylcyanoacrylate); PBuOx, 2-butyl-2-oxazoline; PC, phosphatidylcholine; PCL, poly(ε-caprolactone); PEG, poly(ethylene glycol); PEI, poly(ethyleneimine); PEO, poly(ethylene oxide); PET, position emission tomography; PEtOx, poly(2-ethyl-2-oxazoline); PD, Parkinson's disease; Pgp, P-glycoprotein; PK, pharmacokinetics; PLA, polylactic acid; PLGA, poly(D,L-lactic-co-glycolide); PMeOx, poly(2-methyl-2-oxazoline); POx, poly(2-oxazoline)s; PS, phosphatidylserine; PPG, polypropylene glycol; PPO, poly(propylene oxide); RAP, receptor associated protein; RDP, Rabies virus glycoprotein-derived peptide; rhIDU, α-L-iduronidase; sCAR, cell surface coxsackie-adenovirus receptor; s.c., subcutaneous; Shh, sonic hedgehog; sMTf, soluble melanotransferrin; SOD, superoxide dismutase; SOPE, N-succinyldioleoylphosphatidylethanolamine; TAT, trans-activating transcriptional activator; TBI, traumatic brain injury; TJ, tight junctions; TfR, transferrin receptor; TNFR, tumor necrosis factor decoy receptor; TPGS, α-tocopheryl polyethylene glycol succinate; VLDL, very-low-density lipoprotein.

* Corresponding authors at: Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, NC 27599, USA. Tel.: +1 919 962 1010; fax: +1 919 962 9922.
E-mail addresses: xiang_yi@unc.edu (X. Yi), akabanov@email.unc.edu (A.V. Kabanov).

http://dx.doi.org/10.1016/j.jconrel.2014.06.017
0168-3659/

1. Introduction

Protein therapeutics has made significant progress during the past 30 years, beginning with the invention of the first recombinant protein used in clinical practice, a human insulin [1]. Since then, development of protein therapeutics has been one of the biotech's most notable successes. In recent years, the number of protein-based therapeutics reaching the marketplace has increased exponentially. As of today, more than 130 proteins or peptides are used in clinics and many more are in development [2]. The currently marketed proteins include enzymes, antibodies, clotting factors, anticoagulants, modern insulins, growth hormone, follicle-stimulating hormone, hematopoietic growth factors, interferons, interleukins and others. The market of the therapeutic proteins holds tremendous potential for future growth and it is estimated that by the end of 2018, it may reach the mark of US $165 billion as new products may enter the sector. As patents on first-generation proteins wind down, the industry seeks to protect their markets by introducing protein delivery technologies that provide for improved stability, bioavailability and safety of the therapeutic proteins. Such technologies aim to overcome obstacles to the clinical application of the proteins due to a lack of desirable attributes for adequate absorption or distribution. It therefore becomes critical to incorporate proteins in safe, stable and efficacious delivery systems. Because proteins face formidable enzymatic and penetration barriers, efficient protein delivery to its destination in the body remains a very challenging if not a formidable task.

There is a tremendous potential to develop protein therapeutics for the treatment of neurological and neurodegenerative disorders. Examples include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), human immunodeficiency virus 1 (HIV-1)-associated dementia (HAD) (or more generally HIV-associated cognitive dysfunction), multiple sclerosis (MS), lysosomal storage disorders (LSDs; Gaucher's disease, Niemann–Pick disease, Tay–Sachs disease and Sandhoff's disease, Krabbe's disease, Fabry's disease, metachromatic leukodystrophy amongst nearly 50 total disorders) and others. Other diseases associated with the central nervous system (CNS) include brain tumors, stroke, traumatic brain injury (TBI), and metabolic disorders. Some examples of potential protein therapeutics to treat these CNS related disorders include enzymes in LSDs, antibodies in AD and brain tumors, neurotrophic factors in PD and stroke, and gut–brain hormones in obesity.

Clinical use of these proteins, however, is extremely challenging because of the unique and complex environment imposed by the CNS. Systemic delivery of proteins to the brain inevitably encounters two major hurdles: the rapid serum clearance and the limited penetration at the blood–brain barrier (BBB). Some protein molecules, such as neurotrophic factors can cross the BBB to some extent but are rapidly cleared from the blood, whereas others, such as antibodies, are stable and long circulating in blood but absolutely not permeable at the BBB. In both cases systemic delivery of proteins does not allow to attain their sufficient brain concentration for effective treatment. Proteins can also access the brain through alternative delivery routes that allow bypassing the BBB, such as intracerebroventricular (i.c.v.), intraparenchymal, intranasal (i.n.) or intrathecal (i.t.) administration. However, in most cases the brain uptake of proteins following such administration routes is still surprisingly low, especially in the targeted brain regions where protein therapeutics needs to be delivered. It has been gradually accepted that serious biological barriers are associated with each of these alternative delivery routes.

Therefore a great deal of effort has been dedicated to developing the drug delivery systems and approaches that could help protein molecules crossing numerous barriers on their way to the site of action in the brain. Multiple drug delivery strategies were explored in the attempts to address this challenge. For example, chemical modification of proteins with poly(ethylene glycol) (PEG), known as PEGylation [3], or incorporation of proteins into poly(D,L-lactic-co-glycolide) (PLGA) particles [4,5] increased stability and bioavailability of certain proteins and resulted in development of the Food and Drug Administration (FDA) approved products for various peripheral diseases. However, neither of these technologies has shown much promise so far in delivering protein therapeutics to the brain for treatment of CNS related diseases. Several specific molecules (antibodies, peptides, etc.) that can target and cross BBB through intrinsic transport systems available in brain endothelium were identified and conjugated to protein of interest to create targeted therapeutic agents for CNS related diseases. However, no such conjugate has progressed far enough to enter clinical trials