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Delivery of peptide and protein drugs over the bloodâ€“brain barrier

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Abstract

Peptide and protein (P/P) drugs have been identified as showing great promises for the treatment of various neurodegenerative diseases. A major challenge in this regard, however, is the delivery of P/P drugs over the bloodâ€“brain barrier (BBB). Intense research over the last 25 years has enabled a better understanding of the cellular and molecular transport mechanisms at the BBB, and several strategies for enhanced P/P drug delivery over the BBB have been developed and tested in preclinical and clinicalâ€“experimental research. Among them, technology-based approaches (comprising functionalized nanocarriers and liposomes) and pharmacological strategies (such as the use of carrier systems and chimeric peptide technology) appear to be the most promising ones. This review combines a comprehensive overview on the current understanding of the transport mechanisms at the BBB with promising selected strategies published so far that can be applied to facilitate enhanced P/P drug delivery

over the BBB.

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Abbreviations

5-HT_{1A}, 5-hydroxytryptamine-1A; 6-OHDA, 6-hydroxydopamine; AÎ², Î²-amyloid; ABC, ATP-binding cassette; AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; ADNF, activity-dependent neurotrophic factor; ADNP, activity-dependent neurotroprotective protein; AGRP, agouti-related protein; AIDS, acquired immunodeficiency syndrome; ALS, amyotrophic lateral sclerosis; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ANP, atrial natriuretic peptide; Apo, apoliprotein; APP, amyloid precursor protein; ATP, adenosine triphosphate; AVP, arginine vasopressin; BACE, Î²-APP-cleaving enzyme; BBB, bloodâ€“brain barrier; BCEC, brain capillary endothelial cell; BCRP, breast cancer resistant protein; Bâ€“CSF-B, bloodâ€“cerebrospinal fluid barrier; BDNF, brain-derived neurotrophic factor; BNP, brain natriuretic peptide; BTB, bloodâ€“tumor barrier; BSA, bovine serum albumin; BW, body weight; C, complement; CART, cocaine and amphetamine regulated transcript; CBP, cyclic adenosine monophosphate response element-binding protein; CBSA, cationized BSA; CDK-5, cyclin-dependent kinase-5; CGCs, cultured cerebellar granule cells; CAG, cytosineâ€“adenineâ€“guanosine; cAMP, cyclic adenosine monophosphate; CAT, cationic amino acid transporter; CDDS, chemical drug delivery systems; ChAT, choline acetyltransferase; CINC, cytokine-induced neurotrophil chemoattractant; CNTF, ciliary neurotrophic factor; CRH, corticotropin releasing hormone; CSF, cerebrospinal fluid; CNS, central nervous system; COMT, catechol-O-methyltransferase; Cu/Zn SOD1, copper/zinc superoxide dismutase; EGF, epidermal growth factor; D1, dopamine-1 receptor; DA, dopamine agonist; DMSO, dimethylsulfoxide; DPDPE, [2*6-dimethyl-Tyr1,$_D$, -Pen2,$_D$-Pen5]enkephalin; DSIP, delta-sleep inducing peptide; EAAT, excitatory amino acids transporter; EAE, experimental autoimmune encephalitis; ECS, extracellular space; EGF, epidermal growth factor; ENT_1, equilibrative nitrobenzylthioinosine-sensitive transporter; ENT_2, equilibrative nitrobenzylthioinosine-insensitive transporter; EPO, erythropoietin; fALS, familial ALS; FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid; GDNF, glial-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GHRH, growth hormone releasing hormone; GLP-1, glucagon-like peptide-1; GLUT1, glucose transporter 1; GM1, monosialoganglioside galactose; GM-CSF, granulocyte/monocyte colony stimulating factor; GnRH, gonadotropin releasing

hormone; GSK-3, glycogen synthase kinase-3; Î³-GTP, Î³-glutamyltranspeptidase; HD, Huntington's disease; HDAC, histone deacetylase; HIV, human immunodeficiency virus; Ig, immunoglobulin; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; IL-1Î², interleukin-1 beta; IMS, Intercontinental Medical Statistics; LAT, large neutral amino acid transporter; LDL, low-density lipoprotein; L-DOPA, levodopa; LHRH, luteinizing hormone-releasing hormone; LIF, leukemia inhibitory factor; LTP, long-term potentiation; LUV, large unilamellar vesicle; MAO-B, monoamine oxidase type B; MARK, microtubule affinity regulating kinase; mGluR3, metabotropic glutamate receptor; MCH, melanin concentrating hormone; MCT, monocarboxylate transporters; MDR, multidrug resistance; MIF-1, melanotropin release-inhibiting factor; MIP, macrophage inflammatory protein; MLV, multilamellar large vesicle; mPEG-PLA, methoxypoly(ethylene)glycol-PLA; mPEG-PLGA, methoxypoly(ethylene)glycol-PLGA; MPP, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRP, multidrug resistant protein family; MS, multiple sclerosis; NAAG, N-acetylaspartylglutamate; NGF, nerve growth factor; NK, neurokinin; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NPY, neuropeptide tyrosine; NSAID, nonsteroidal anti-inflammatory drug; NT, neurotrophin; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; ODN, oligonucleotide; PACA, poly(alkyl)cyanoacrylate; PACAP, pituitary adenylate cyclase activating polypeptide; PBCA, (poly)butylcyanoacrylate; PD, Parkinson's disease; PEG, polyethylene glycol; PEG-PHDCA, PEGylated poly(hexadecyl)cyanoacrylate; PEI, polyethyleneimine; PEO, poly(ethylene oxide); P-gp, P-glycoprotein; PHCA, (poly)hexylcyanoacrylate; PHI, peptide histidine-isoleucine; PLA, poly(D, ,L-lactic acid); PLGA, poly(D, ,L-lactide-co-glycolic acid); PMA, phorbol myristate acetate; PMMA, poly(methyl)methacrylate; P/P drugs, peptide and protein drugs; PTS, peptide transport system; PYY, peptide tyrosineâ€“tyrosine; RGD, arginineâ€“glycineâ€“aspartic acid; REV, reverse phase evaporation vesicle; rhLIF, recombinant leukemia inhibitory factor; SAHA, suberoylanilide hydroxamic acid; sALS, sporadic ALS; SC, solute carrier; SDS, sodium dodecyl sulfate; SP, substance P; SUV, small unilamellar vesicle; TEER, trans-epithelial electric resistance; TH, tyrosine hydroxylase; TNF, tumor necrosis factor; TRH, thyrotropin releasing hormone; UHDRS, unified HD rating scale; UPDRS, unified PD rating scale; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal peptide

Keywords

Bloodâ€“brain barrier; Delivery strategies; Neurodegenerative diseases; Neurotherapeutics; Peptide- and protein-drug targeting; Pharmacotherapy; Therapeutic strategies

strategies

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