Indian Journal of Pharmacy and Pharmacology 2020;7(4):213–221

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Pharmacy and Pharmacology

Journal homepage: https://www.ijpp.org.in/

Review Article

Nano-carriers for brain disorders targeting the blood brain barrier (BBB) crossing strategies

Shalaka Dabhekar[1], Madhura Dixit[1], Milind J Umekar[1], Krishna R Gupta[1,*]

[1] *Smt Kishoritai Bhoyar College of Pharmacy, Kamptee, Maharashtra, India*

ARTICLE INFO

Article history:
Received 28-12-2020
Accepted 31-12-2020
Available online 25-01-2021

Keywords:
Nanocarriers
CNS diseases
Blood brain barrier
Interruption in BBB
Nanoneurology

ABSTRACT

The blood brain barrier (BBB) segregates the central nervous system from the systemic circulation nevertheless also retard the effective treatment of central nervous system diseases. Intrinsically, the BBB prevents contagions and pathogens by invade the brain, but also restraint the brain uptake of therapeutic molecules. The potentiality to treat central nervous system disorders is strongly limited by the poor access of many therapeutic agent to the target tissues, formed by a complex interplay of endothelial cells, astrocyte and pericytes and the cells are connected by tight junctions which express a variety of receptors, transporters, and pores which allow the penetration of specific substances from the blood into the CNS through which only selected molecules can passively diffuse to reach the brain. Nonetheless, under certain pathological conditions, the BBB is interrupted by allowing direct interaction between blood components and consequently, it plays a pivotal role in minimizing CNS toxin exposure, controlling immune–CNS communication, maintaining a low protein CNS environment, separating peripheral and CNS neuro-signals, and importantly, regulating ion homeostasis. At present, along with the structural and mechanistic manifestation of the BBB under physiological and pathological conditions it is feasible to design drug delivery systems that could cross the BBB adequately. This review focuses on strategies that influence such BBB disruption for delivering nano-carriers to the central nervous system with wider implementations and broader prospection the treatment of brain targeted therapy, nano-medicines have turn out to be more potent, more distinct and less toxic than traditional drug therapy.

1. Introduction

Disorders related to the central nervous system including Alzheimer's disease, Parkinson's disease, strokes, brain tumour and psychosisare the world's leading causes of infirmities associated with various comorbidities and thus have been invite more scrutiny for the targeted and effective therapy of all the above mentioned disorders.[1,2] Although, very few drugs are advantageous for the treatment of the CNS affected diseases and the therapeutic efficacy is greatly limited by various factors, among which inefficient transportation of drugs across the BBB is the most promising challenge.[3–5] Central nervous system comprising of brain which is the major portion for regulation of the nerve impulses throughout the periphery as well as within the brain and the structural phenomenon of it was well known for the its lipophilicity and the barriers present in the brain i.e., blood brain barriers.[6,7] The ability of drug molecule to transport across the BBB greatly depends on the properties of hydrophilicity of the drug, hydrophobicity, dissociation degree, and molecular size of the drug particle due to which the transportation process of the drug molecule may carried out without hampering any alterations or disturbance to the brain environment.[8–10] Consequently, the evolution of drug delivery systems that can effectively transport the curative agents into the CNS is of critical importance in the targeted treatment of CNS diseases. Recently, nano-materials have been considered as versatile drug transportation systems

* *Corresponding author*.
E-mail address: krg1903@gmail.com (K. R. Gupta).

https://doi.org/10.18231/j.ijpp.2020.035

across BBB, which can deliver the loaded diagnostics and therapeutic agents into the central nervous system. Various types of nano-materials serve the unparalleled advantages such as relatively high drug loading content, good stability, controllable release of the active drug, excellent passive and active targeting, biodegradability, biocompatibility, and low toxicity.[9] Moreover, approaches avoiding uptake by the reticulo-endothelial system (RES) allow drug-loaded nano-materials to have a prolonged blood circulation, which significantly improves the BBB-crossing possibilities of nano-materials resulting in a relatively high drug accumulation in the brain parenchyma for desirable theranostic effects of the drug.[9,11–13] The primary advantage of Nanoparticles carrier technology is that NPs mask the blood-brain barrier limiting characteristics of the therapeutic drug molecule and because of this, system may slow drug release in the brain, decreasing peripheral toxicity. Depending upon the nanotechnologies, many strategies were extensively exploited for the transportation of effective drug agents across the BBB, for example, receptors-mediated transcytosis, disruption of BBB with mechanical or ultrasound, and intranasal delivery of nano-materials. The above discussed characteristics of the nano-materials could affect the transportation ability across the BBB, which provides tremendous space for researchers to investigate and develop more promising strategies for nanomaterial-based BBB crossing.[14–19] In this review, we will come up with the latest progress in nanomaterial based BBB crossing strategies for the treatment of CNS diseases and its associated comorbidities and the mechansims.

2. Blood Brain Barriers

The blood–brain barrier (BBB) is a selective semipermeable lining of endothelial cells that prevents the solutes in the circulating blood from non-selectively crossing into the extracellular fluid of the CNS where neurons reside and are also a physical and metabolic barrier that limits transportation between the blood and neural tissues, comprising of astrocyte end-feet encasing the capillary, and pericytes embedded in the capillary basement membrane which allows the passage of some molecules by passive diffusion, as well as the selective transport of various nutrients, ions, organic anions, and macromolecules such as glucose, water and amino acids that are essential for neuronal functions.[8,20] It maintained the stability of physiological environment of brain tissues and prevent the CNS from infraction caused by harmful agents or contagions in the blood. Furthermore these are the major source for transporting the drug molecule to the site of action with respect to the functional therapeutic efficacy of the drug which should be decided according to the diseases condition of the brain. The disorders of the CNS may be directly depend upon the mechanism of action of any particular drug should interact firstly with these barriers to lead the purpose. Figure 1 is showing the schematic illustration of blood brain barrier.[21,22] Most of the therapeutic agents delivered into the brain should pass through the endothelial cells alternatively the transportation of the ions and solutes crossing BBB carried out via the paracellular passage between these endothelial cells and the transportation of many cargos across the BBB takes place via transcellular passage on the endothelial cells which is also named as transcytosis. Precisely to maintained healthy environment of the brain there should be rigid balance between the paracellular and transcellular pathways.[23] In recent times the transcellular pathway has been broadly explored and various strategies have been designed for the transportation of the therapeutic agents into the brain tissues as this pathway generally allows passive diffusion of small lipophilic molecules having the size of < 500 Dalton.

3. Blood Brain Barriers and CNS Diseases

CNS diseases have been increasing in the world while the development of targeted therapy for the prevention is greatly limited because of the BBB. Many strategies based on nanomaterials have been established to overcome the BBB for the treatment of CNS diseases. Including this the BBB and targeting potential of the nanomaterials towards the CNS diseases like Alzheimer's disease, Stroke, Parkinson's disease, Brain tumour, Autism and Schizophrenia are presented.[24]Figure 2 showing the associated diseases of central nervous system in correlation with blood brain barrier dysfunctioning.[25,26] To reach the specific site of action in the brain the need of targeted dug delivery is prerequisite and hence the role on nano technology for the treatment of followed CNS disorders found to be very important. According to the disease pathophysiology and the mechanism of the drug action should followed the penetration from the brain barriers by binding to the blood and with this it will efficiently reach to the site after the drug molecule is entrapped with the nano materials.[27]

4. Role of Blood Brain Barriers in Various CNS Disorders

4.1. Alzheimer's disease

Modified BBB transport of Alzheimer's neurotoxin amyloid -peptide (A) between blood with brain and brain with blood, atypical angiogenesis, brain hypo-perfusion and neurovascular inflammation, may initiate or contribute to a circularity of the disease process, resulting in progressivedys function of synaptic and neuronal regions and loss in Alzheimer's disease (AD).[28–31] BBB plays a major role in Alzheimer's disease. On the basis of the neurovascular hypothesis, decreased BBB clearance of Aβ is one of the main reasons that may induce increased amyloid load in the brain and the indicating Alzheimer's disease.[32,33] In concern with pericytes, astrocytes and

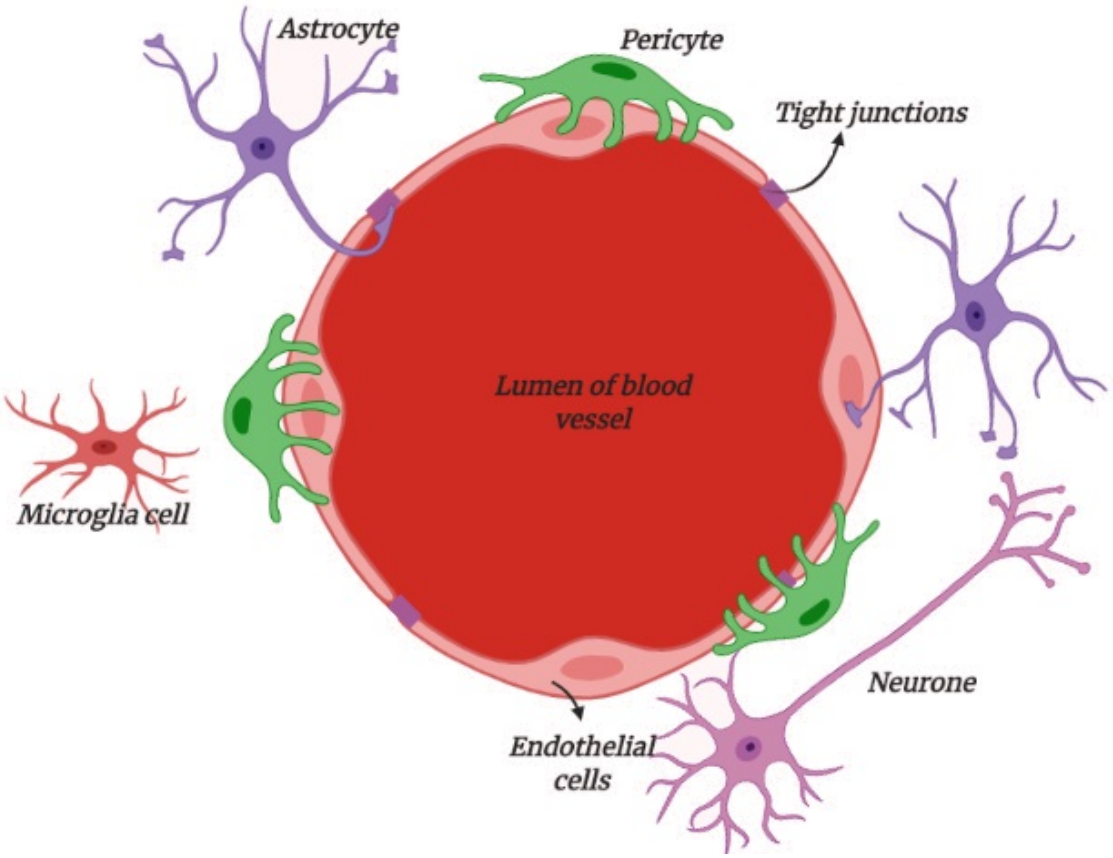

Fig. 1: Schematic illustration of blood brain barrier

microglia, the BBB separates components of the circulating blood from neurons and the BBB maintains the chemical composition of the neuronal 'milieu' that means the proper and constant environment of brain kept by neurones and also which is required for proper functioning of neuronal circuits, synaptic transmission, synaptic modifications, angiogenesis and neurogenesis in the adult brain.[34]

4.2. Parkinson disease

The comorbidities associated to the blood brain barrier disruption inducing the disease state of parkinsonism with the physiological conditions like inflammation of astrocytes, infiltration of T-leukocytes, and microgliosisin the brain of affected individual is related to the permeability of BBB and loss of dopaminergic neurons moreover as the lot of pro-inflammatory cytokines of TNF-α, IL-1β and interferon-γ are released, and ROS and NO are greatly produced in microglia and astrocytes of such PD patients, which are thought to be correlated with BBB impairment.[35–39] In this condition there is selective degeneration of dopaminergic neurons in substantianigra leads to the depletion of dopamine in striatum with the presences of lewy bodies in neurons which are composed of α-synuclein and protein inclusions.[40–42] The correlation between the progressive BBB damage and the pathology course has been indicated by the difference of the albumin ratios in parkinsonian brain, also there are some associations between cerebral blood flow deficiencies, vascular modifications and the loss of BBB integrity in striatum and substantia nigra of PD patients.[43–45]

4.3. Strokes

The most common type of stroke or ischemic stroke, is defined as obstruction of blood flow to part of the brain due to a thrombus or blood clot, condition of cerebral edema (brain swelling)as this may lead to breakdown of BBB, reassembly of endothelial cell tight junctions and this results in a one year patient survival rate of 60% because of the brain lacks blood supply during the stroke episodes due to a bleeding vessel of hemorrhagic stroke or vessel occlusion of ischemic stroke induced by a blood clot.[39,46,47] Evidences of pathophysiology of this condition causes the deprivation of oxygen and nutrients in both hemorrhagic stroke and ischemic stroke leads to brain cell

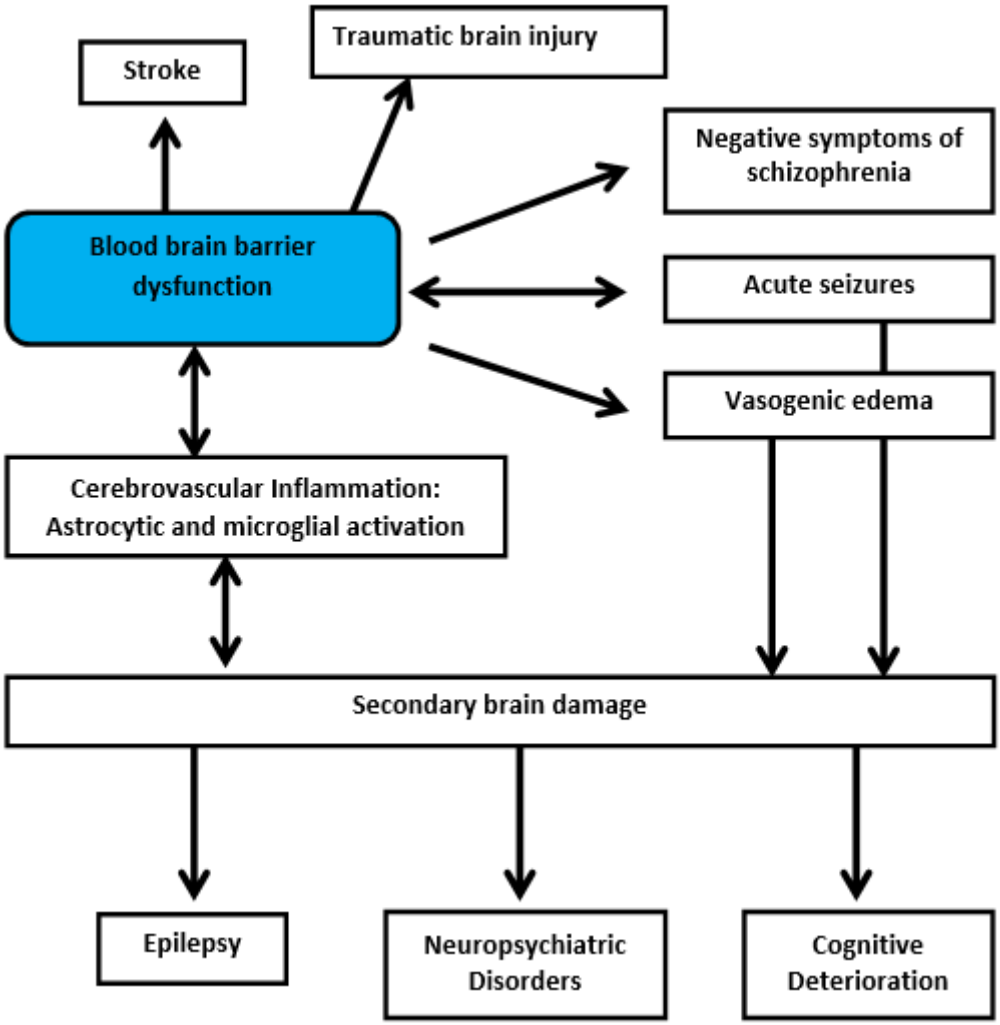

Fig. 2: Overview of Blood brain barrier associated with CNS disorders

death, dysfunction of neurons and ultimate death of patient furthermore throughout the episode of ischemic stroke there is short opening time ranging from minutes to hours, followed by the refractory interval take place to the BBB, subsequently the BBB may undergo an reopening with time period of hours to days.[48,49] Thus the reopening of BBB is directly associated with the formation of edema, reduce the cerebral injury via blood re-supply, and the endothelium activation, recruitment of leukocyte, production of cytokine and ROS. In this condition of stroke drug delivery should consider the compromised tight junctions, and the initial and late opening of the BBB while taking the advantage of the BBB-opening time window and the receptors expressed on the luminal side of endothelial cells may be helpful for the BBB-crossing of nanoparticles.[50]

4.4. Brain tumour

Glioblastoma (GB) has been thought to be the most frequent primary brain tumor and the state of tumour in the brain state a heterogeneous group of primary and metastatic neoplasms in CNS which have a superlative poor prognosis and very low survival rate of patients.[51] It has been an evolution in the research term of brain tumour therapy as there is very challenging aspects because of the complex and heterogeneous molecular biology, which leads to different prognosis of patients expose to the same treatment strategies.[52,53] Primary brain tumours (PBT) refers to the malignancies that originate and localised within the brain. Although from a primary cancer that is affected in other parts of the body first but later on it get invade the CNS by producing inflammation or by affecting with any carcinogen that are spread through primary cancer such as lung cancer, breast cancer, colorectal cancer, renal cell cancer or melanomas outside of the central nervous

system and from here the initiation of metastatic brain tumour is begin.[54] Consequently due to complex and critical structural anatomy of the blood brain barrier, transportation of anticancer agents loaded nano-materials across BBB is still the great challenge in the treatment of brain tumours also the properties and the design strategies of nanoparticles (NPs) mostly depend on the type of cancer, development stage, and infected tissue location.[55–57]

4.5. Psychosis

Altered blood–brain barrier function is a central factor in the pathophysiology of many CNS disorders among psychosis is the leading disorder associated with various comorbidities.[58] The blood–brain barrier is formed by the endothelium of brain micro-vessels affected by adjacent cells and has several important functions which are correlatewith the disease condition in psychosis. The endothelium delivers oxygen and nutrients like glucose, amino acids, and other neurotransmitter precursors to the brain subsequently removes waste products, and severely restricts the permeability of highly toxic and neuro-active agents and pathogens.[59,60] At both the blood–brain barrier and the choroid plexus, tight junctions between adjacent cells restrict diffusion of polar solutes through the intercellular cleft that is considered as paracellular pathway.[61] The pathophysiology of psychosis related to the Blood–brain barrier or the neurovascular unit changes in pathology can include altered expression of ion channels and drug transporters on endothelial cells and glia, increased leakiness of tight junctions and extravasation of plasma proteins, up-regulation of luminal adhesion molecules, and increased adhesion and transmigration of leucocytes.[62,63] New methodologies are suggested for studying the blood–brain barrier function in psychosis which areenlisted as:

1. Dynamic contrast-enhanced MRI for in vivo measurement of blood–brain barrier permeability
2. PET ligands for in vivo measurement of blood–brain barrier permeability (eg, 2-amino-[3-^{11}C] iso-butyric acid)
3. In vitro blood–brain barrier models derived from induced pluripotent stem cells from patients
4. Measurement of peripheral antibodiesto CNS-restricted antigens (eg, anti-S100B antibodies) as a marker of chronic blood–brain barrier disruption
5. Measurement of the effects of manipulations of psychosis-associated genetic loci on blood–brain barrier structure and function in animal models
6. Large-scale multicentre studies providing large sample sizes, and examination of associations between psychosis risk factors and markers of blood–brain barrier disruption
7. Integration and identification of measures of blood–brain barrier integrity across different modalities (eg, combining serum levels of S100B and magnetic resonance spectroscopy measures of candidate neural metabolites).

5. Nanomaterial Based BBB Crossing Mechanism

The BBB is essential for the maintenance of the unique neuro-parenchymal environment but it also represents an invulnerable obstacle for a multiplicity of therapeutically important drugs as there is permeation factor of these active drug constituents is take into consideration.[64] Drugs that are intended to act in the CNS can be administered systemically, if they have the ability to overcome the blood–brain barrier (BBB), or have to be introduced directly in the CNS by invasive methods, if such avoidance is limited.[65] Although this barrier is composed of different cell types such as endothelial cells, pericytes, astrocytes, and microglial cells there is specific permeation mechanism of blood brain barriers with respect to their crossing pathways as shown in the figure (Figure 3). The nanomaterial-based BBB crossing mechanisms can be classified into two categories: 1) invasive mechanism; 2) non-invasive mechanism in which for the invasive mechanism, the BBB needs to be opened via physical means, and the nano-materials are transported across the BBB through paracellular pathway and with this the temporary BBB disruption strategy and local delivery strategy belong to the invasive mechanism, which is also called paracellular mechanism. Likewise for the non-invasive mechanism, the BBB is intact during the drug delivery process, and the nano-materials are delivered across the BBB via transcellular pathway known as transcellular mechanism.

6. New Strategies Targeted for Nanoparticles to Enhance Brain Drug Delivery

Pharmaceutical compounds may not be able to approach the brain while circulating in blood due to the presence of the blood brain barriers that limits entry into the brain and protects it from infections or harmful substances whereas these barriers allows for the diffusion of a limited portion of substances and prevents the diffusion of even small molecules into the brain.[66] While many essential molecules are able to diffuse across this barrier but it frequently excludes therapeutic compounds given their special properties. Moreover, these nano compounds pass through this barrier and reach neurons through different routes and give the essential theranostic effects on the diseased brain.[67] Several Nanoparticles have been used for crossing the BBB as these NPs penetrates through the tight junctions between the endothelial cells of the vessels and enable the drug to pass through the BBB. Endocytosis and transcytosis of NPs can also facilitate drug transfer through

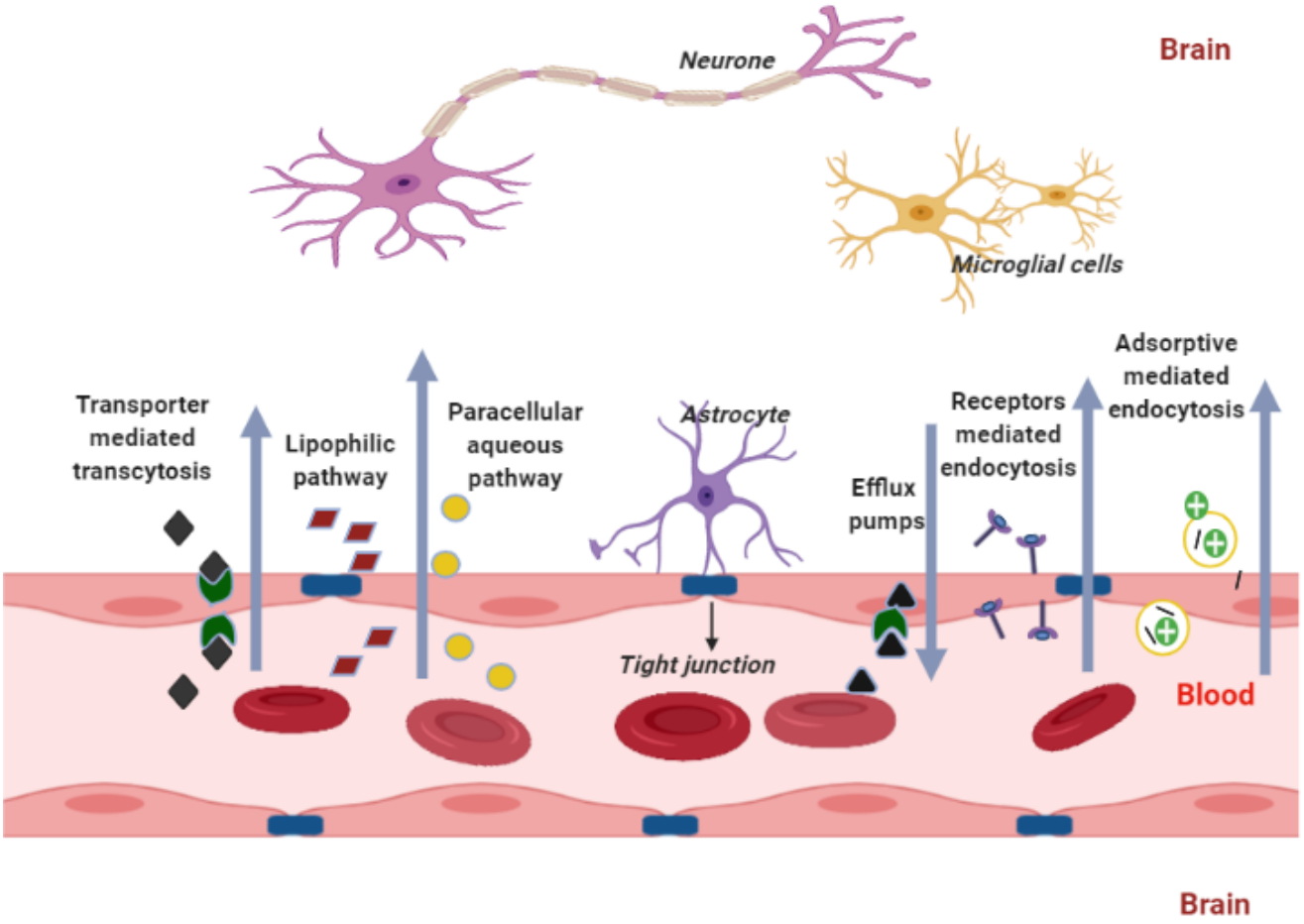

Fig. 3: Permeation mechanism of blood brain barrier

the endothelial cell layer. NPs can target specific cells by conjugating or coating ligands, and by use of specific ligands can transport across the BBB from the circulation by receptor-mediated transcytosis. The lipophilic features of lipid NPs enable them to cross the BBB to enter the brain through multiple transport pathways, including paracellular pathway, transcellular pathway, transcytosis, and receptor mediated endocytosis all these are responsible for the transporting pathways for the nano-materials.[68,69] The latest strategies of nanotechnology with the enhancement of drug delivery in the brain is shown in Figure 4. Known to be paracellular and across cells which is transcellular. This passive diffusion accounts for the transport of solutes through the cell membrane, depending upon size and lipophilicity of the substances.[70] Carrier mediated transport (CMT) or carrier-mediated influx are forms of diffusion which may be passive or active, depending on the context, and involve the unidirectional transport of drugs from the blood to the brain. It is mainly instrumental in the transport of many essential polar molecules, with the help of carrier systems or transporters, such as glucose, amino acids and nucleosides into the brain.

Receptor mediated transport is mainly implement in the transportation of macro-molecules like peptides and proteins across the BBB by conjugating the substance with ligands such as lactoferrin, transferrin and insulin.[57–59] Although it is an important transport mechanism of predominant interest in drug delivery to the central nervous system. Likewise the adsorptive mediated transport is a type of endocytosis induced by conjugating the particle to cationised ligands or peptides such as albumin.[71,72] The general principle of AME based upon the transport is electrostatic interaction between a positively charged substance (cationized peptide-albumin) and the negatively charged sites on the brain endothelial cell (BEC) surface (e.g. glycoprotein).

According to the current scenario in the evolution of drug delivery system targeting for the prevention of central nervous system and blood brain barrier disorders with respect to the newer strategies are developed to target such

Fig. 4: Development of new strategies based on NP's technology for drug delivery to the brain

brain associated disorders and for this the nanocarriers have to serve as good candidates for drug delivery across the BBB possessing various characteristic features that are summarized as follows.[73,74]

1. Particle diameter less than 100 nanometers;
2. Non-toxic, biodegradable and biocompatible;
3. Stable in blood (i.e., no opsonisation by proteins);
4. BBB-targeted (i.e., use of cell surface, ligands, and receptor mediated endocytosis);
5. No activation of neutrophils, non-inflammatory;
6. No platelet aggregation;
7. Avoidance of the reticulo-endothelial systems;
8. Prolonged circulation time;
9. Scalable and cost effective with regard to manufacturing process;
10. Amenable to small molecules, peptides, proteins or nucleic acids;
11. Controlled drug release or should exhibit modulation of drug release profiles.

7. Conclusion

The BBB plays a very important role in maintaining normal physiological function of CNS. With the rapid evolution of nano-biotechnology, nano-medicine has shown great potential in the therapeutics and diagnostics of neurological disorders, although the mechanism of many brain pathologies is still not fully exemplify, the leading reason is thought to be the BBB disruption. Therefore, more rudimentary studies on the nanomaterial-based BBB crossing strategies and drug release in the brain regions still require to be carried out in more details. In this review paper we learn about the strategies involve in the crossing of drug molecule in the brain via penetrating through the brain barriers and hence we can explore a broader prospect and a promising direction of nanomaterial-mediated BBB-crossing for the treatment of CNS diseases in the future.

8. Source of Funding

None.

9. Conflict of Interest

None.

References

1. Nazem A, Mansoori GA. Nanotechnology Solutions for Alzheimer's Disease: Advances in Research Tools, Diagnostic Methods and Therapeutic Agents. *J Alzheimer's Dis*. 2008;13(2):199–223. doi:10.3233/jad-2008-13210.
2. Srikanth M, Kessler JA. Nanotechnology—novel therapeutics for CNS disorders. *Nat Rev Neurol*. 2012;8(6):307–18. doi:10.1038/nrneurol.2012.76.
3. Sweeney MD, Sagare AP, Zlokovic BV. Cerebrospinal Fluid Biomarkers of Neurovascular Dysfunction in Mild Dementia and Alzheimer'S Disease. *J Cereb Blood Flow Metab*. 2015;35(7):1055–68. doi:10.1038/jcbfm.2015.76.
4. Vijayan M, Reddy PH. Vascular dementia, and Alzheimer's disease: molecular links. *J Alzheimer's Dis*. 2016;54:427–43.
5. Reddy PH, Tonk S, Kumar S, Vijayan M, Kandimalla R, Kuruva CS, et al. A critical evaluation of neuroprotective and neurodegenerative MicroRNAs in Alzheimer's disease. *Biochem Biophys Res Commun*. 2017;483(4):1156–65. doi:10.1016/j.bbrc.2016.08.067.
6. Vilella A, Ruozi B, Belletti D, Pederzoli F, Galliani M, Semeghini V, et al. Endocytosis of Nanomedicines: The Case of Glycopeptide Engineered PLGA Nanoparticles. *Pharm*. 2015;7(2):74–89. doi:10.3390/pharmaceutics7020074.
7. Gao H, Pang H, Jiang X. Targeted delivery of nano-therapeutics for major disorders of the central nervous system. *Pharm Res*. 2013;30:2485–98.
8. Dong X. Current strategies for brain drug delivery. *Theranostics*. 2018;8:1481–93.
9. Chen Y, Liu L. Modern methods for delivery of drugs across the blood-brain barrier. *Adv Drug Deliv Rev*. 2012;64:640–65.
10. Betzer O, Shilo M, Opochinsky R, Barnoy E, Motiei M, Okun E, et al. The effect of nanoparticle size on the ability to cross the blood–brain barrier: an in vivo study. *Nanomedicine*. 2017;12(13):1533–46. doi:10.2217/nnm-2017-0022.
11. Baratta MG. Getting to the brain. *Nat Nanotechnol*. 2018;13:536.
12. Bender E. Getting cancer drugs into the brain. *Nat*. 2018;561:46–7.
13. Wolak DJ, Thorne RG. Diffusion of Macromolecules in the Brain: Implications for Drug Delivery. *Mol Pharma*. 2013;10(5):1492–1504. doi:10.1021/mp300495e.
14. Zhang N, Yan F, Liang X, Wu M, Shen Y, Chen M, et al. Localized delivery of curcumin into brain with polysorbate 80-modified cerasomes by ultrasound-targeted microbubble destruction for improved Parkinson's disease therapy. *Theranostics*. 2018;8:2264–77.
15. Ivask A, Pilkington EH, Blin T, Käkinen A, Vija H, Visnapuu M, et al. Uptake and transcytosis of functionalized superparamagnetic iron oxide nanoparticles in an in vitro blood brain barrier model. *Biomat Sci*. 2018;6(2):314–23. doi:10.1039/c7bm01012e.
16. Tsai YC, Vijayaraghavan P, Chiang WH, Chen HH, Liu TI, Shen MY, et al. Targeted Delivery of Functionalized Upconversion

Nanoparticles for Externally Triggered Photothermal/Photodynamic Therapies of Brain Glioblastoma. *Theranostics*. 2018;8(5):1435–48. doi:10.7150/thno.22482.
17. Patel T, Zhou J, Piepmeier JM, Saltzman WM. Polymeric nanoparticles for drug delivery to the central nervous system. *Adv Drug Deliv Rev*. 2012;64(7):701–5. doi:10.1016/j.addr.2011.12.006.
18. Feng Q, Shen Y, Fu Y, Muroski ME, Zhang P, Wang Q, et al. Self-assembly of gold nanoparticles shows microenvironmentmediated dynamic switching and enhanced brain tumor targeting. *Theranostics*. 2017;7:1875–89.
19. Lin HC, Ho MY, Tsen CM, Huang CC, Wu CC, Huang YJ, et al. From the cover: comparative proteomics Reveals silver nanoparticles alter fatty acid metabolism and amyloid beta clearance for neuronal Apoptosis in a Triple cell coculture model of the blood-brain barrier. *Toxicol Sci*. 2017;158:151–63.
20. Zhao Z, Nelson AR, Betsholtz C, Zlokovic BV. Establishment and Dysfunction of the Blood-Brain Barrier. *Cell*. 2015;163(5):1064–78. doi:10.1016/j.cell.2015.10.067.
21. Abbott NJ. Dynamics of CNS Barriers: Evolution, Differentiation, and Modulation. *Cell Mol Neurobiol*. 2005;25(1):5–23. doi:10.1007/s10571-004-1374-y.
22. Stewart PE. Endothelial vesicles in the blood-brain barrier: are they related to permeability? *Cell Mol Neurobiol*. 2000;20:149–63.
23. Cooper I, Last D, Guez D, Sharabi S, Goldman SE, Lubitz I, et al. Combined Local Blood–Brain Barrier Opening and Systemic Methotrexate for the Treatment of Brain Tumors. *J Cereb Blood Flow Metab*. 2015;35(6):967–76. doi:10.1038/jcbfm.2015.6.
24. Li W, Sharma M, Kaur P. The DrrAB Efflux System of Streptomyces peucetius Is a Multidrug Transporter of Broad Substrate Specificity. *J Biol Chem*. 2014;289(18):12633–46. doi:10.1074/jbc.m113.536136.
25. On N, Miller D. Transporter-Based Delivery of Anticancer Drugs to the Brain: Improving Brain Penetration by Minimizing Drug Efflux at the Blood-Brain Barrier. *Curr Pharm Des*. 2014;20(10):1499–1509. doi:10.2174/13816128113199990458.
26. Li W, Rao DK, Kaur P. Dual Role of the Metalloprotease FtsH in Biogenesis of the DrrAB Drug Transporter. *Journal of Biological Chemistry*. 2013;288(17):11854–11864. Available from: https://dx.doi.org/10.1074/jbc.m112.441915. doi:10.1074/jbc.m112.441915.
27. Erickson MA, Banks WA. Blood–Brain Barrier Dysfunction as a Cause and Consequence of Alzheimer's Disease. *J Cereb Blood Flow Metab*. 2013;33(10):1500–13. doi:10.1038/jcbfm.2013.135.
28. Zlokovic BV. Neurovascular mechanisms of Alzheimer's neurodegeneration. *Trends Neurosci*. 2005;28(4):202–8. doi:10.1016/j.tins.2005.02.001.
29. Donahue JE, Flaherty SL, Johanson CE, Duncan JA, Silverberg GD, Miller MC, et al. RAGE, LRP-1, and amyloid-beta protein in Alzheimer's disease. *Acta Neuropathol*. 2006;112(4):405–15. doi:10.1007/s00401-006-0115-3.
30. Wijesuriya HC, Bullock JY, Faull RLM, Hladky SB, Barrand MA. ABC efflux transporters in brain vasculature of Alzheimer's subjects. *Brain Res*. 2010;1358:228–38. doi:10.1016/j.brainres.2010.08.034.
31. Owen JB, Sultana R, Aluise CD, Erickson MA, Price TO, Bu G, et al. Oxidative modification to LDL receptor-related protein 1 in hippocampus from subjects with Alzheimer disease: Implications for Aβ accumulation in AD brain. *Free Radical Biol Med*. 2010;49(11):1798–1803. doi:10.1016/j.freeradbiomed.2010.09.013.
32. van Assema D, Lubberink M, Bauer M, van der Flier W, Schuit RC, Windhorst AD, et al. Blood–brain barrier P-glycoprotein function in Alzheimer's disease. *Brain*. 2012;135(1):181–9. doi:10.1093/brain/awr298.
33. Sengillo JD, Winkler EA, Walker CT, Sullivan JS, Johnson M, Zlokovic BV. Deficiency in Mural Vascular Cells Coincides with Blood-Brain Barrier Disruption in Alzheimer's Disease. *Brain Pathol*. 2013;23(3):303–10. doi:10.1111/bpa.12004.
34. Sagare AP, Bell RD, Zhao Z, Ma Q, Winkler EA, Ramanathan A, et al. Pericyte loss influences Alzheimer-like neurodegeneration in mice. *Nat Commun*. 2013;4(1):2932. doi:10.1038/ncomms3932.
35. Fernandez HH. Updates in the medical management of Parkinson disease. *Clevel Clin J Med*. 2012;79:28–35.
36. Pisani V, Stefani A, Pierantozzi M, Natoli S, Stanzione P, Franciotta D, et al. Increased blood-cerebrospinal fluid transfer of albumin in advanced Parkinson's disease. *J Neuroinflammation*. 2012;9(1):188–9. doi:10.1186/1742-2094-9-188.
37. Gray MT, Woulfe JM. Striatal Blood–Brain Barrier Permeability in Parkinson'S Disease. *J Cereb Blood Flow Metab*. 2015;35(5):747–50. doi:10.1038/jcbfm.2015.32.
38. Cabezas R, Avila M, Gonzalez J, El-BachÃ¡RS, ez EB, a Segura LMG, et al. Astrocytic modulation of blood brain barrier: perspectives on Parkinson's disease. *Front Cell Neurosci*. 2014;8:211. doi:10.3389/fncel.2014.00211.
39. Kyle S, Saha S. Nanotechnology for the Detection and Therapy of Stroke. *Adv Healthcare Mat*. 2014;3(11):1703–20. doi:10.1002/adhm.201400009.
40. Barcia C, Bautista V, Bahillo A, Fernández-Villalba E, Faucheux B, Poza MP, et al. Changes in vascularization in substantia nigra pars compacta of monkeys rendered parkinsonian. *J Neural Transmission*. 2005;112(9):1237–48. doi:10.1007/s00702-004-0256-2.
41. Rite I, Machado A, Cano J, Venero JL. Blood-brain barrier disruption induces in vivo degeneration of nigral dopaminergic neurons. *J Neurochem*. 2007;101(6):1567–82. doi:10.1111/j.1471-4159.2007.04567.x.
42. Bradaric BD, Patel A, Schneider JA, Carvey PM, Hendey B. Evidence for angiogenesis in Parkinson's disease, incidental Lewy body disease, and progressive supranuclear palsy. *J Neural Transmission*. 2012;119(1):59–71. doi:10.1007/s00702-011-0684-8.
43. Wong D, Dorovini-Zis K, Vincent SR. Cytokines, nitric oxide, and cGMP modulate the permeability of an in vitro model of the human blood–brain barrier. *Exp Neurol*. 2004;190(2):446–55. doi:10.1016/j.expneurol.2004.08.008.
44. Bartels AL. Blood-brain barrier P-glycoprotein function in neurodegenerative disease. *Curr Pharm Des*. 2011;17:2771–7.
45. Jangula A, Murphy EJ. Lipopolysaccharide-induced blood brain barrier permeability is enhanced by alpha-synuclein expression. *Neurosci Lett*. 2013;551:23–7. doi:10.1016/j.neulet.2013.06.058.
46. Kumar A, Aakriti, Gupta V. A review on animal models of stroke: An update. *Brain Res Bull*. 2016;122:35–44. doi:10.1016/j.brainresbull.2016.02.016.
47. Jiao H, Wang Z, Liu Y, Wang P, Xue Y. Specific role of tight junction proteins claudin-5, occludin, and ZO-1 of the blood-brain barrier in a focal cerebral ischemic insult. *J Mol Neurosci*. 2011;44:130–9.
48. Kulik T, Kusano Y, Aronhime S, Sandler AL, Winn HR. Regulation of cerebral vasculature in normal and ischemic brain. *Neuropharmacol*. 2008;55(3):281–8. doi:10.1016/j.neuropharm.2008.04.017.
49. Yang Y, Estrada EY, Thompson JF, Liu W, Rosenberg GA. Matrix Metalloproteinase-Mediated Disruption of Tight Junction Proteins in Cerebral Vessels is Reversed by Synthetic Matrix Metalloproteinase Inhibitor in Focal Ischemia in Rat. *J Cereb Blood Flow Metab*. 2007;27(4):697–709. doi:10.1038/sj.jcbfm.9600375.
50. Khatri R, McKinney AM, Swenson B, Janardhan V. Blood-brain barrier, reperfusion injury, and hemorrhagic transformation in acute ischemic stroke. *Neurol*. 2012;79(Issue 13, Supplement 1):S52–7. doi:10.1212/wnl.0b013e3182697e70.
51. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol*. 2016;131(6):803–20. doi:10.1007/s00401-016-1545-1.
52. Preusser M, de Ribaupierre S, Wöhrer A, Erridge SC, Hegi M, Weller M, et al. Current concepts and management of glioblastoma. *Ann Neurol*. 2011;70(1):9–21. doi:10.1002/ana.22425.
53. Jendrossek V, Belka C, Bamberg M. Novel chemotherapeutic agents for the treatment of glioblastoma multiforme. *Exp Opin Investig Drugs*. 2003;12(12):1899–1924. doi:10.1517/13543784.12.12.1899.
54. Pang HH, Chen PY, Wei KC, Huang CW, Shiue YL, Huang CY, et al. Convection-enhanced delivery of a virus-like nanotherapeutic agent with dualmodal imaging for besiegement and eradication of brain tumors. *Theranostics*. 2019;9:1752–63.

55. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO Classification of Tumours of the Central Nervous System. *Acta Neuropathol*. 2007;114(2):97–109. doi:10.1007/s00401-007-0243-4.
56. ud Din F, Aman W, Ullah I, Qureshi OS, Mustapha O, Shafique S, et al. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. *Int J Nanomed*. 2017;12:7291–7309. doi:10.2147/ijn.s146315.
57. Tang W, Fan W, Lau L, Deng L, Shen Z, Chen X. Emerging blood-brain-barrier crossing nanotechnology for brain cancer theranostics. *Chem Soc Rev*. 2019;48:2967.
58. Bramini M, Ye D, Hallerbach A, Raghnaill MN, Salvati A, Åberg C, et al. Imaging Approach to Mechanistic Study of Nanoparticle Interactions with the Blood–Brain Barrier. *ACS Nano*. 2014;8(5):4304–12. doi:10.1021/nn5018523.
59. Gorter JA, van Vliet E, Aronica E. Status epilepticus, blood–brain barrier disruption, inflammation, and epileptogenesis. *Epilepsy Behav*. 2015;49:13–6. doi:10.1016/j.yebeh.2015.04.047.
60. Qosa H, Miller DS, Pasinelli P, Trotti D. Regulation of ABC efflux transporters at blood-brain barrier in health and neurological disorders. *Brain Res*. 2015;1628:298–316. doi:10.1016/j.brainres.2015.07.005.
61. Bodor N, Buchwald P. Brain-Targeted Drug Delivery. *Am J Drug Deliv*. 2003;1(1):13–26. doi:10.2165/00137696-200301010-00002.
62. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *Lancet Psychiatry*. 2015;2(3):258–70. doi:10.1016/s2215-0366(14)00122-9.
63. Demjaha A, Egerton A, Murray RM, Kapur S, Howes OD, Stone JM, et al. Antipsychotic Treatment Resistance in Schizophrenia Associated with Elevated Glutamate Levels but Normal Dopamine Function. *Biol Psychiatry*. 2014;75(5):e11–3. doi:10.1016/j.biopsych.2013.06.011.
64. Shen Z, Wu H, Yang S, Ma X, Li Z, Tan M, et al. A novel Trojan-horse targeting strategy to reduce the non-specific uptake of nanocarriers by non-cancerous cells. *Biomater*. 2015;70:1–11.
65. Shen Z, Chen T, Ma X, Ren W, Zhou Z, Zhu G, et al. Multifunctional theranostic nanoparticles based on exceedingly small magnetic iron oxide nanoparticles for T1-weighted magnetic resonance imaging and chemotherapy. *ACS Nano*. 2017;11:10992–11004.
66. Begley DJ. Delivery of therapeutic agents to the central nervous system: the problems and the possibilities. *Pharmacol Ther*. 2004;104(1):29–45. doi:10.1016/j.pharmthera.2004.08.001.
67. Chen Y, Dalwadi G, Benson H. Drug Delivery Across the Blood-Brain Barrier. *Curr Drug Deliv*. 2004;1(4):361–76. doi:10.2174/1567201043334542.
68. Hawkins BT, Davis TP. The Blood-Brain Barrier/Neurovascular Unit in Health and Disease. *Pharmacol Rev*. 2005;57(2):173–85. doi:10.1124/pr.57.2.4.
69. Brightman MW, Reese TS. Junctions between intimately apposed cell membranes in the vertebrate brain. *J Cell Biol*. 1969;40(3):648–77. doi:10.1083/jcb.40.3.648.
70. Fischer H, Gottschlich R, Seelig A. Blood-Brain Barrier Permeation: Molecular Parameters Governing Passive Diffusion. *J Membrane Biol*. 1998;165(3):201–11. doi:10.1007/s002329900434.
71. Roberts RL, Fine RE, Sandra A. Receptor-mediated endocytosis of transferrin at the blood-brain barrier. *J Cell Sci*. 1993;104(2):521–32.
72. Kumagai AK, Eisenberg JB, Pardridge WM. Absorptive-mediated endocytosis of cationized albumin and a beta-endorphin-cationized albumin chimeric peptide by isolated brain capillaries. Model system of blood-brain barrier transport. *J Biol Chem*. 1987;262(31):15214–9. doi:10.1016/s0021-9258(18)48160-4.
73. Lockman PR, Mumper RJ, Khan MA, Allen DD. Nanoparticle Technology for Drug Delivery Across the Blood-Brain Barrier. *Drug Dev Ind Pharmacy*. 2002;28:1–13. doi:10.1081/ddc-120001481.
74. Olivier JC. Drug Transport to Brain with Targeted Nanoparticles. *NeuroRX*. 2005;2(1):108–19.

Author biography

Shalaka Dabhekar, Lecturer

Madhura Dixit, Assistant Professor

Milind J Umekar, Principal

Krishna R Gupta, Professor

Cite this article: Dabhekar S, Dixit M, Umekar MJ, Gupta KR. Nano-carriers for brain disorders targeting the blood brain barrier (BBB) crossing strategies. *Indian J Pharm Pharmacol* 2020;7(4):213-221.