Using nanoparticles to facilitate penetration of the blood-brain barrier for drug delivery

Joseph Bello MS; Rand Swenson MD, PhD

Dartmouth GEISEL SCHOOL OF MEDICINE

Introduction

- The BBB is made up a number of structures; endothelial cells bound together via **tight junctions** (TJs), **parenchymal cells**, **astrocyte end-feet**, and a **basement membrane** [1].
- Transport across the BBB can be broken down into two main types: paracellular and transcellular [2].
  - **Paracellular**: Between cells; mostly small ions/solutes
  - **Transcellular**: Through cells; hydrophobic molecules (diffusion), proteins/lipophobic molecules (receptors)
- These transport mechanisms can be "hacked" by nanoparticles to facilitate delivery of therapeutics or other molecules.

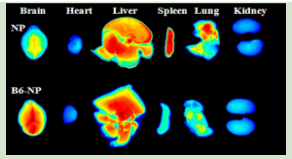
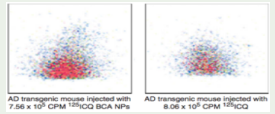
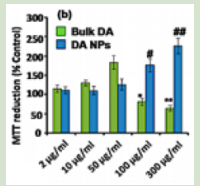
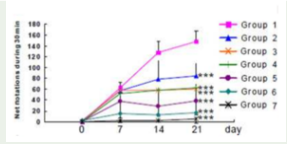
Background

Nanoparticles can either be **synthetic** or **natural**; synthetic NPs can either be **polymeric** (ex/ polylactic acid, polyethylenimine, dendrimers, etc.) or **inorganic** (ex/ gold, silica), while natural NPs are made from natural materials such as polysaccharides, amino acids, and proteins (ex/ albumin, chitosan).

NPs can be modified in a variety of different ways, which is what makes them useful and promising for the future of drug delivery. NPs can be made in specific shapes (rods, spheres, squares, disks, etc.) which can penetrate the BBB in different ways.

One study for example, found that polystyrene gold nanorods coated with anti-body showed a 7-fold increase of accumulation in brain tissue in mouse models when compared to their nanosphere counterparts [6]. Some other things that can be modified include the size, the charge of the NP, the method of drug delivery (ex/ covalent binding, adsorption, entrapment) and the ligands that can be bound to the surface of the NP to help it bypass the BBB.

Results

Source	Method	Results
[7]	**PEGylated polylactic acid NPs** • Modified with a transferrin-like ligand (B6) • Loaded with a known neuroprotective molecule (NAPVSIPQ) • **(Liu et al)**	 • Significant increase in brain accumulation, Decrease in peripheral accumulation
[8]	**Quinoline-n-butyl-cyanoacrylate-based NPs** • Loaded with I-CQ; a radioactive β-amyloid affinity drug • **(Kulkarni et al)**	 • Significant increase in the penetration of the BBB when bound to the NPs
[9]	**Poly lactic-co-glycolic acid (PLGA) NPs** • Loaded with dopamine for delivery across the BBB • **(Pahuja et al)**	 • Allowed for controlled release and therefore reduced toxicity-related side-effects
[10]	**Lactoferrin-modified NPs** • Loaded with a neurotrophic factor gene (hGDNF) • **(Huang et al)**	 • Significant improvement in the locomotor activity of the PD mice models

Conclusion

To my knowledge, there are currently no ongoing clinical trials for new neurotherapeutics using NP delivery across the BBB, although these systems have shown great promise in animal models. The BBB, particularly in humans, is a very intricate and complex system that is nearly impermeable without the right measures being taken to facilitate passage. As can be seen from the outcomes of the articles reviewed above and many others, nanomedicine and nanoparticles specifically have proven that they have a large role to play in future of brain drug delivery, due both to their high modification potential and unique properties. Further research and understanding of the mechanisms of the BBB are required, but the future of brain drug delivery is an exciting one.

References

[1] M.J. Cipolla, Barriers of the CNS, in: D.N. Granger, J. Granger (Eds.), Cereb. Circ, Mor- gan & Claypool Life Sciences, San Rafael (CA), 2009 (http://www.ncbi.nlm.nih.gov/ pubmed/21452434).

[2] H. Wolburg, A. Lippoldt, Tight junctions of the blood–brain barrier: development, composition and regulation, Vasc. Pharmacol. 38 (2002) 323–337, http://dx.doi. org/10.1016/S1537-1891(02)00200-8.

[3] N.J. Abbott, A.A.K. Patabendige, D.E.M. Dolman, S.R. Yusof, D.J. Begley, Structure and function of the blood–brain barrier, Neurobiol. Dis. 37 (2010) 13–25, http://dx.doi. org/10.1016/j.nbd.2009.07.030.

[4] Cláudia Saraiva, Catarina Praça, Raquel Ferreira, Tiago Santos, Lino Ferreira, Liliana Bernardino, Nanoparticle-mediated brain drug delivery: Overcoming blood–brain barrier to treat neurodegenerative diseases, In Journal of Controlled Release, Volume 235, 2016, Pages 34-47

[5] Y.Persidsky, S.H.Ramirez, J.Haorah, G.D.Kanmogne, Blood–brain barrier: structural components and function under physiologic and pathologic conditions, J. NeuroImmune Pharmacol. 1 (2006) 223–236, http://dx.doi.org/10.1007/s11481- 006-9025-3.

[6] P. Kolhar, A.C. Anselmo, V. Gupta, K. Pant, B. Prabhakarpandian, E. Ruoslahti, et al., Using shape effects to target antibody-coated nanoparticles to lung and brain endothelium, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 10753–10758, http://dx.doi. org/10.1073/pnas.1308345110.

[7] Z. Liu, X. Gao, T. Kang, M. Jiang, D. Miao, G. Gu, et al., B6 peptide-modified PEG-PLA nanoparticles for enhanced brain delivery of neuroprotective peptide, Bioconjug. Chem. 24 (2013) 997–1007, http://dx.doi.org/10.1021/bc400055h.

[8] P.V. Kulkarni, C.A. Roney, P.P. Antich, F.J. Bonte, A.V. Raghu, T.M. Aminabhavi, Quinoline-n-butylcyanoacrylate-based nanoparticles for brain targeting for the diagnosis of Alzheimer's disease, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 2 (2010) 35–47, http://dx.doi.org/10.1002/wnan.59

[9] R. Pahuja, K. Seth, A. Shukla, R.K. Shukla, P. Bhatnagar, L.K.S. Chauhan, et al., Trans- blood brain barrier delivery of dopamine loaded nanoparticles reverses functional deficits in parkinsonian rats, ACS Nano (2015)http://dx.doi.org/10.1021/ nn506408v

[10] R. Huang, L. Han, J. Li, F. Ren, W. Ke, C. Jiang, et al., Neuroprotection in a 6- hydroxydopamine-lesioned Parkinson model using lactoferrin-modified nanoparticles, J. Gene Med. 11 (2009) 754–763, http://dx.doi.org/10.1002/jgm.1361.