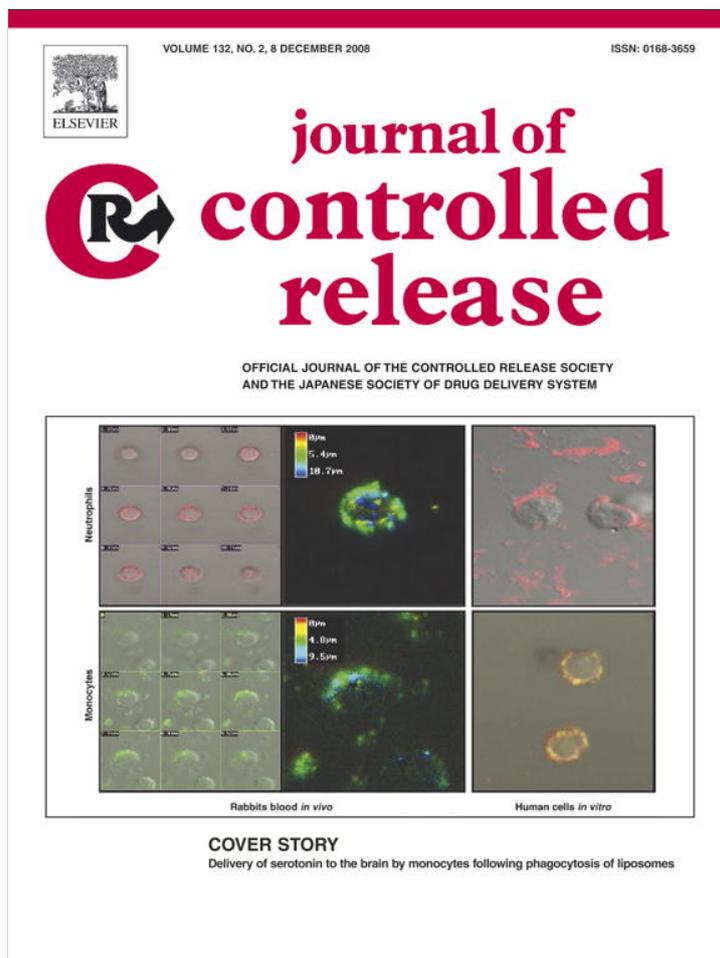


Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Contents lists available at ScienceDirect

Journal of Controlled Release

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

Cover Story

Trojan monocytes for improved drug delivery to the brain

One of the major limiting factors in the development of new drugs for brain diseases is the blood–brain barrier (BBB). In an elegant work in this issue [1], Afergan et al. have shown that circulating monocytes can be exploited as a transporter of drugs to the brain. The authors hypothesized that phagocytic cells of the innate immune system, mainly neutrophils and monocytes, could be exploited as a transporter of drugs to the brain. Their hypothesis stems from two observations. First, the brain is under immunological surveillance. Second, partial and transient depletion of circulating monocytes was obtained by particulate delivery systems (liposomes or polymeric nanoparticles) of bisphosphonates, which selectively inactivate and kill these cells following effective phagocytosis.

Nanoparticulate drug delivery systems have been used to avoid the mononuclear phagocytic system (MPS, formerly known as the reticuloendothelial system) and achieve longer circulation time for enhanced tissue uptake. The most common approaches used for escaping MPS are formulating the particles with neutral surface charge; hydrophilic masking of the membrane (e.g., PEGylation); and using ultra small size nanoparticles (<80 nm). Afergan et al., however, took quite an unusual approach of enhancing phagocytosis by monocytes. They reasoned that effective phagocytosis by monocytes in the circulation could be achieved by the so-called 'conventional' liposomes which are negatively charged and relatively large, i.e., not ultra small. An interesting finding in this study is that activated monocytes are responsible for transporting negatively-charged liposomes to the brain under normal physiologic conditions in animals, leading to two folds higher drug concentration than a free drug. After phagocytosis of liposomes, monocytes, just like Trojan horses, transport their cargo into the brain. The vesicles discharge their encapsulated drug following lysosomal action that disrupts the liposome bilayer, and the released drug is distributed in the brain tissues.

Using the Trojan monocytes, one can deliver virtually any drugs to the brain. The drug to be delivered can be hydrophobic or hydrophilic low molecular weight drugs, gene constructs, and peptides or proteins. One important thing to note here is that liposomes or polymer nanoparticles are targeted to the MPS system, and thus the drug biodistribution is restricted to cells/organs of the MPS only. The clinical relevance of the study is apparently limited at this point, since only 2-fold higher uptake of serotonin was obtained. An order of magnitude or more of brain uptake may be necessary for delivery of therapeutically effective amount of a drug. Nevertheless, this Trojan monocyte approach provides a new possibility of more effective treatment of brain-associated inflammatory disorders, including multiple sclerosis and in Alzheimer's disease, which are characterized with increased passage of immune cells across the BBB.

Reference

- [1] Eyal Afergan, Hila Epstein, Rachel Dahan, Nickolay Koroukhov, Keren Rohekar, Haim D. Danenberg, Gershon Golomb, Delivery of serotonin to the brain by monocytes following phagocytosis of liposomes, *J. Control. Release* 132 (2008) 84–90. doi:10.1016/j.jconrel.2008.08.017.

Kinam Park
Purdue University,
Departments of Biomedical Engineering and Pharmaceutics,
Indiana, USA
E-mail address: kpark@purdue.edu.