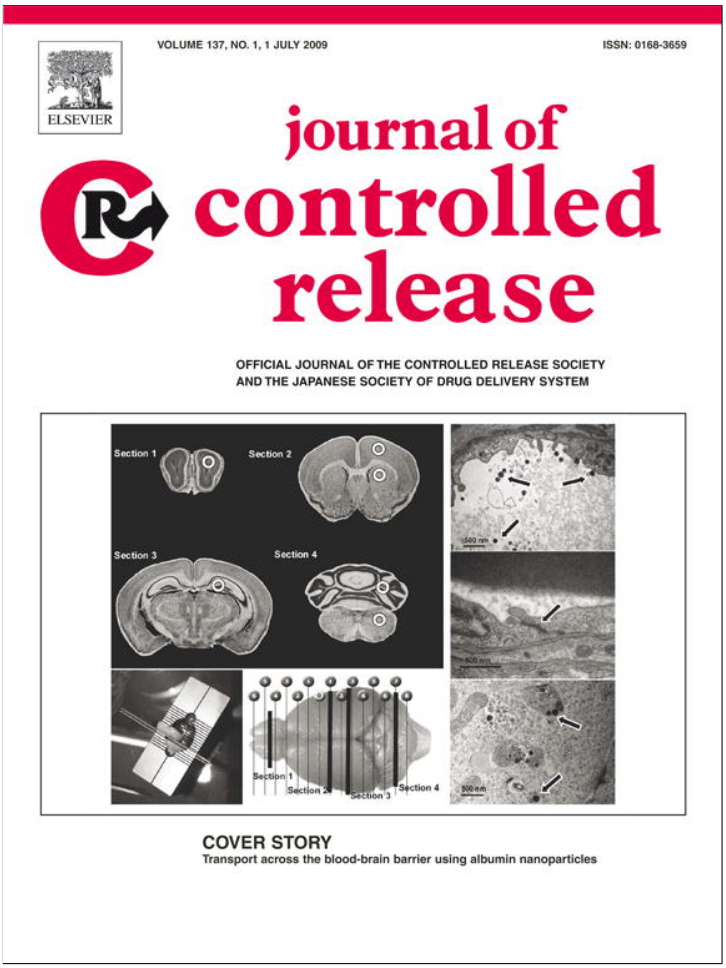

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Cover Story

Transport across the blood-brain barrier using albumin nanoparticles

Drug delivery to the brain has been severely limited for both small and large molecules due to the presence of the blood-brain barrier (BBB), formed by the capillary endothelial cells of the brain vasculature. Many different strategies have been historically tried to improve drug delivery to the central nervous system (CNS). One successful strategy employed to enable the brain delivery of these molecules has been the use of nanoparticles. Details of the mechanism by which delivery is achieved, however, have been open to question. The article in this issue by Professor Kreuter and his group has provided information on the mechanism for the first time [1]. They designed albumin nanoparticles with apolipoprotein E (Apo E) attached on the surface (Apo E-albumin nanoparticles). After intravenous administration, Apo E-albumin nanoparticles are internalized into the brain capillary endothelial cells. This is followed by transcytosis and release into brain parenchyma and the subsequent appearance of these particles in the cytoplasm of neurons. This observation provides a strong evidence of a mechanism enabling the direct delivery of the albumin-bound drugs to the central neuronal targets.

Previously, it was argued by some authors that the delivery of drugs to the CNS by nanoparticles and subsequent marked central effect was a result of permeabilizing the BBB and a relaxation of the tight junctions. The work by Professor Kreuter in this issue, however, clearly shows that albumin nanoparticles move directly across the BBB with a retained integrity of tight junctions, as demonstrated by a preserved barrier to ionic lanthanum. Thus, Apo E-albumin nanoparticles provide a mechanism for bypassing the BBB and for direct delivery of drugs to the brain. These observations are also supported by *in vitro* studies with a mouse endothelial BBB cell line. Control experiments where Apo E is not attached to the albumin nanoparticles do not support a process of transcytosis and direct delivery to the brain for these untargeted particles. Clearly the mechanism involves binding to an Apo E receptor present at the blood-facing surface of the BBB which is able to induce receptor-mediated transcytosis. This particle transport is presumably utilising the mechanism present in the BBB which normally delivers LDL to the brain. The cross-linked albumin forming the main component of these particles retains a number of reactive functional groups to which a wide range of drugs and macromolecules could be attached for brain delivery. The study by Professor Kreuter and his group has laid the foundation to develop highly efficient vehicles for drug delivery to the brain by overcoming the BBB.

Reference

[1] A. Zensi, D. Begley, C. Pontikis, C. Legros, L. Mihoreanu, S. Wagner, C. Büchel, H. von Briesen, J. Kreuter, Albumin nanoparticles targeted with ApoE enter the CNS by transcytosis and are delivered to neurons, J. Control. Release 137 (2009) 78–86.

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