INVOLVEMENT OF MOUSE OATP1A4 IN THE UPTAKE OF ORGANIC ANIONS ACROSS THE BLOOD-BRAIN BARRIER

Atsushi Ose, Hiroyuki Kusuhara, Chihiro Endo and Yuichi Sugiyama
Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan

The blood-brain barrier (BBB) restricts the distribution of drugs in the central nervous system. A multispecific organic anion transporter, Oatp1a4 is expressed in both the abluminal and the luminal membrane of rat brain capillary endothelial cells. Based on kinetic studies, we have suggested that Oatp1a4 plays a major role in the efflux of pitavastatin, a novel HMG-CoA reductase inhibitor (statin), through the BBB in rats. However, its luminal localization suggests that Oatp1a4 may also be involved in the uptake of its substrate compounds from the systemic circulation into the brain. The purpose of the present study was to characterize the uptake of pitavastatin into the brain across the BBB using the in situ brain perfusion technique. The uptake clearance of pitavastatin was 50 μl/min/g brain. The uptake of pitavastatin by the brain was saturable with a Km value of 0.3 μM, and the saturable component accounts for the major part of the total uptake. Digoxin (Oatp1a4 specific inhibitor) and taurocholate (Oatp inhibitor) significantly inhibited the uptake of pitavastatin in a concentration-dependent manner, while p-aminohippurate (Oat inhibitor) had no effect. In addition to pitavastatin, an in situ brain perfusion study of another statin, pravastatin, was also performed. The uptake clearance of pravastatin was lower than that of pitavastatin (12 μl/min/g brain), but it was not saturable and digoxin had no effect on it. These results suggest that there is an uptake system for organic anions that accepts statins at the BBB, and Oatp1a4 is a candidate transporter.


INVOLVEMENT OF OCTN2 IN TISSUE DISTRIBUTION OF ORGANIC CATIONS

Tadakatsu Nakamura, Yoshiyuki Kubo, Yukio Kato and Akira Tsuji
Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa 920-1192, Japan

Many cationic drugs are highly distributed to various tissues and subjected to renal secretion. We have identified organic cation/carnitine transporter OCTN2 which transports not only carnitine, but also various organic cations including tetraethylammonium (TEA), verapamil and mepyramine. We have shown that OCTN2 plays an important role in renal distribution and secretion of TEA, a typical organic cation, although it has not yet been clarified whether OCTN2 is important in the disposition of other cationic drugs. The aim of this study was to clarify the involvement of OCTN2 in the tissue distribution of organic cations. The H1-receptor antagonist mepyramine was intravenously injected in juvenile visceral steatosis (jvs) mice lacking the function of OCTN2, and wild mice, followed by determination of plasma and tissue concentrations with HPLC. In jvs mice, heart and pancreas exhibited higher tissue-to-plasma concentration ratio (kp) than those in wild mice. In addition, heart slices of jvs mice showed the higher uptake activity and lower efflux of mepyramine, compared with wild mice. These results suggest that OCTN2 is involved in distribution of cationic drugs to certain tissues, and, especially in the heart, OCTN2 may act as an efflux transporter for cationic drugs. Considering that several types of cationic drugs exhibit serious side-effects in heart, OCTN2-mediated efflux may be important as a barrier to protect this organ from exposure to those drugs. Further analyses are underway to investigate possible involvement of OCTN2 in tissue distribution of other H1-receptor antagonists.