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Cover Story

Insight into brain-targeted drug delivery via LAT1-utilizing prodrugs



Despite the recent development of the promising brain drug delivery approaches, the blood-brain barrier (BBB) remains the main obstacle preventing the transport of neuroprotective drug candidates into the brain. One potential means to overcome this hurdle is to utilize specific transporters available at the BBB with a prodrug approach. In particular, L-type amino acid transporter (LAT1) carrying large, branched neutral amino acids from systemic circulation into the brain has been shown to be efficient in the prodrug delivery through the BBB [1]. LAT1 is selectively expressed on both luminal and abluminal brain capillary membranes as well as the membrane of cells of the brain parenchyma [2–4]. Thus, LAT1 is a good candidate for targeted drug delivery into the brain with a few benefits, such as the ability to transport drugs through the BBB avoiding other organs, and the carrier-mediated intracellular delivery [5]. Several prodrugs utilizing LAT1 have been developed and they were shown to bind to the transporter *in vitro* and reach the brain *in vivo* [5–9]. The information about systemic distribution of these prodrugs, however, is limited.

The paper of Puris et al. in the current issue is focused on investigation of the structure-pharmacokinetics relationship for five LAT1-utilizing prodrugs of ketoprofen, a cyclooxygenase inhibitor [10]. The study provides insights into the systemic distribution of the prodrugs and the organ-specific release of the parent drug. The LAT1-mediated uptake *in vitro*, penetration rate, systemic pharmacokinetics in mice and the ability of prodrugs to release ketoprofen in the mouse brain were studied and compared in terms of structural and physicochemical properties of the compounds. The structural features of LAT1-utilizing prodrugs ensuring the highest brain delivery and release of ketoprofen in the brain with reduced peripheral distribution were identified. Moreover, the authors explored the possibility to predict the brain and systemic pharmacokinetics of the prodrugs using the data from early stage experiments.

The study of Puris et al. provides tools for targeted brain delivery of central nervous system (CNS) drugs. The structure-pharmacokinetics relationship analysis suggests that the presence of an aromatic ring in the promoiety of the prodrugs facilitates the LAT1-binding ability and utilization of the transporter *in vitro*. Moreover, the meta- or para-conjugation of an aromatic promoiety directly to ketoprofen ensures the brain delivery of the parent drug with higher ratios of the brain to plasma and brain to liver distribution. On the other hand, the aliphatic promoiety, or addition of carbon attached to the aromatic promoiety, does not benefit the brain delivery of ketoprofen. Moreover, the study demonstrates that the early stage experiments, such as *in vitro* LAT1 binding, nonspecific tissue binding and *in situ* brain perfusion, enable selection of prodrug candidates for pharmacokinetic studies. The pharmacokinetic profile of prodrugs, however, cannot be predicted due to the lack of information about the intra-brain/systemic distribution of

the prodrugs and the release of the parent drug.

Overall, the study of Puris et al. proves that structural optimization of LAT1-utilizing prodrugs results in the efficient drug delivery into the brain with minimized systemic distribution of a parent drug. Moreover, the paper highlights that brain delivery of transporter-utilizing prodrugs is a complex process, which cannot be predicted from physicochemical properties, BBB permeation and plasma/tissue unbound fraction of the compounds. Therefore, multiple factors affecting the transporter-mediated delivery of the CNS drugs should be taken into account at the early stage of drug development. The real importance of the study by Puris et al. is that it explores targeted drug delivery in its true meaning and reminds us of the importance of research based on reasoning rather than hype.

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