S39-2 Drug response in the central nervos system and efflux system at the blood-brain barrier

◯Hiroyuki KUSUHARA[1], Yuichi SUGIYAMA[1]

[1]Univ. of Tokyo, Grad. Sch. of Pharm. Sci.

The pharmacological action of drugs in the brain is determined by their permeability across the blood-brain barrier (BBB) as well as systemic exposure and protein binding in the blood. The present study examined the role of ABC transporters, BCRP and MRP4, in the blood-brain barrier (BBB) using their knockout mice (KO). Following intravenous administration, the brain-to-plasma concentration ratio ($K_{p,brain}$) of candidate compounds was determined. The $K_{p,brain}$ of phytoestrogenes, such as genistein, and dantrolene, was significantly greater in BCRP KO than that in wild-type mice. The ratio of $K_{p,brain}$ in wild-type to KO represents the BCRP activity at the BBB, which did not exhibit any correlation with the in vitro values determined using BCRP-expressing cells. Since some BCRP substrates are also transported by P-gp, it is likely that P-gp is also involved in the efflux across the BBB, thereby, attenuating the effect of BCRP deficiency. When Ro64-0802, an active form of oseltamivir, was administered subcutaneously, it barely penetrated into the brain in wild-type mice, but the $K_{p,brain}$ was significantly greater in MRP4 KO mice compared with that in wild-type mice. Therefore, both BCRP and MRP4 play significant roles in the BBB to limit the brain penetration of drugs and other xenobiotic compounds from the blood. In addition, the overlapping substrate specificities of P-gp and BCRP suggest that they provide a robust efflux system at the BBB.