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Title of research project	Development of placental permeability evaluation techniques for analyzing species differences
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【Abstract】

Objectives, Fetal toxicity of chemicals are mostly estimated from rat data, however, species differences between rat and human in the placental permeability decrease the reliability of the estimation. The purpose of the present research project is to develop the placental permeability evaluation techniques for analyzing species differences.

Methods, Single arterial injection and perfusion techniques were developed and used for the analysis of placental permeability. Placental brush-border and basolateral membrane vesicles were purified from placental villous tissues and absolute expressions of transporters in these membranes were quantified by using LC-MS/MS.

Results and Consideration, The placental permeability of some compounds tends to be consistent with lipophilicity. However, the placental permeability of some hydrophilic compounds was very high because of the presence of transporter-mediated transfer processes, and the placental permeability of some lipophilic compounds was very low because they are substrates of ABC efflux transporters such as MDR1 and/or BCPR. The effect of ABC efflux transporters on placental permeability of substrates including bisphenol A appears to be lower in human compared with rat, which may influence the species difference in the fetal toxicity. The placental permeability of methylmercury-cysteine conjugate was very low compared with L-leucine, even though L-leucine and methylmercury-cysteine conjugate were both substrates for LAT expressed in the brush-border membrane of the placenta. This is probably because of the differences in the transfer process at the basolateral membrane. The placental permeability of betaine in the fetus-to-mother direction is higher than that in the mother-to-fetus direction, which would be due to the uptake process via SNAT2 at the basolateral membrane of the placental barrier. The human placental barrier expresses several transporters such as GLUT1, ENT1, MCT1, ASCT2, TauT, OATP2B1, OAT4, MDR1, MRP1, and MRP4. Of these transporters, ASCT2, OATP2B1, OAT4, and MRP1 are predominantly expressed at the basolateral membrane, while MDR1 and BCRP are predominantly expressed at the brush-border membrane.

Conclusion, We have developed several techniques for analyzing the placental permeability and the absolute expression levels of transporter proteins. These techniques will help us to understand the species differences in the placental permeability of chemicals.