Editorial

Transporter-Mediated Specific Drug Therapy During Pregnancy

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The placenta forms a selective barrier that functions to transport nutrients and fetal wastes in the appropriate directions. Syncytiotrophoblasts (SCTBT), which form the surface of the placental villi, play an essential role in restricting drug import through the blood-placental barrier (BPB) to the fetus. The apical surface of the SCTBT layer is the maternal-facing membrane, and makes direct contact with the maternal environment, while the basal side of the SCTBT layer faces the fetal environment. Nutrient and waste transport across the SCTBT layer is thought to be regulated by the polarized expression of transporters in the apical or basal membrane. Indeed, polarized expression of transporters, such as P-glycoprotein (P-gp), multidrug resistance protein 2 (MRP2) and L-type amino acid transporter-1 (LAT1), has been reported at the plasma membranes on the maternal blood side in SCTBT cells, and the divalent metal transporter-1 (DMT-1), organic anion transporting polypeptide-B (OATP-B), and MRP1 are expressed at plasma membranes on the fetal blood side of SCTBT cells. It is anticipated that drugs in the maternal circulation will preferentially inhibit the transporters expressed on the apical membrane of SCTBT layers compared with those of the basal membrane, and vice versa. Pregnancy is a dynamic state, and drugs have potential use for curing disorders of the mother or the fetus. According to surveys of drug use during pregnancy, fetuses are exposed to prescription and non-prescription drugs prenatally or perinatally. Therefore, analysis of the placental transport of drugs, nutrients, and fetal wastes is important in connection with normal fetal development and pregnancy.

In the BPB, many transporters play important roles during the development of the fetus and the fetal brain. SCTBT express many nutrient transporters and regulate the transplacental movement of glucose, amino acids, fatty acids, and nucleosides. However, the regulatory mechanisms governing the polarized expression of the transporters, and the interactions between the transporters and drugs are still poorly understood. In vitro experiments using freshly isolated cells, primary cultured cells, and immortalized cell lines are very useful tools for elucidating those transporter functions, as well as the physiological and biological functions of the BPB. We established conditionally immortalized rat SCTBT cell lines (TR-TBT) from transgenic rats harboring the temperature-sensitive simian virus-40 large T-antigen. TR-TBTs express mRNAs of many transporters, including amino acids, neurotransmitter, organic anion and cation, and xenobiotic efflux transporters. Moreover, TR-TBTs exhibit taurine, GABA, and DHEA-S uptake activity. To know the localization of transporters in BPB is important for safe medication in pregnancy. Moreover, it is also important to analyze the mechanism for sorting transporters to apical/basal membranes in the BPB. However, the localizations of many transporters in the BOB are unknown, except for P-gp, MRP1, MRP2, and serotonin transporter (SERT). Further, the mechanism for sorting transporters to the apical/basal membranes remains unclear.

There are some transporter-deficient mice reported, such as TauT, P-gp, and BCRP/ABCG2. P-gp deficient mice show susceptibility to cleft palate in fetal life, so P-gp seems to have an important role in protecting the fetus from potential teratogens. P-gp inhibitors should be carefully evaluated for their potential to increase susceptibility to chemical-induced teratogenesis.

Up to now, the penetration of drugs of BPB has been reported to be high in the perfusion experiments using the placenta immediately after the birth. However, in 2004, it was reported that the diffusion space in the mouse placenta increased dramatically by a factor secreted at the term placenta. It is suggested that the results obtained from the experiments using term placenta may not be a right index of permeability of drugs in the in vivo placenta. There are possibilities that the influx and efflux of drug via transporters may be more important than those via diffusion.

Recently, a comprehensive and precise list of drug transporters in various organs has become available. In future, efficient organ-specific drug delivery should be feasible by appropriately modifying the chemical structure of drugs. I wish to have the drug which is effective to mother, but not effective to fetus, because of organ-specific delivery system in the body, vice versa.

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