**Placental MATE1 Expression in Rats Explains Species Differences in Fetal Transfer of Organic Cations**

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**Background and aims.** Drug transporters expressed at the placental syncytiotrophoblasts may be related to species differences in placental permeability and fetal toxicity of drugs. The fetal-to-maternal concentration ratio (F/M ratio) of metformin, a typical substrate of organic cation transporters, has been reported to be higher in pregnant women than in pregnant rats. In this study, we aimed to investigate the effect of species differences in the organic cation transporter expression on the fetal transfer of organic cations.

**Methods.** Absolute protein expression of organic cation transporter (OCT) 3 and multidrug and toxin extrusion protein (MATE) 1 in human, rat, and mouse placentas was quantified using LC-MS/MS. Pregnant rats and mice were continuously infused with [14C]metformin or [3H]1-Methyl-4-phenylpyridinium (MPP+) via jugular vein and the F/M ratio was measured. Pyrimethamine (2 μmol/kg) was used as a potent inhibitor of MATE1.

**Results.** OCT3 protein expression was detected in human, rat, and mouse placenta. On the other hand, MATE1 protein expression was selectively detected in rat placenta, but not in human and mouse placenta. The F/M ratio of organic cations such as [14C]metformin or [3H]MPP+ was significantly lower in the rat than in the mouse. Preadministration of pyrimethamine (2 μmol/kg), a potent inhibitor of MATE1, increased the F/M ratio of [14C]metformin or [3H]MPP+ in the rat, but not in the mouse, suggesting that the fetal transfer of metformin in the rat is limited by placental MATE1 expression.

**Conclusion/Discussion.** The lower transfer of organic cations to the fetus in the rat is suggested to be due to the selective expression of MATE1 protein in the rat placenta. This information will be helpful in estimating fetal transfer and toxicity of drugs in human fetuses using rat data.