MULTIDRUG AND TOXIN EXTRUSION 1 MEDIATED TUBULAR SECRETION OF VARENICLINE
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[Purpose] In proximal tubules, cationic drugs are taken up from blood into cells by organic cation transporter 2 (OCT2/SLC22A2) and eliminated into the lumen by multidrug and toxin extrusion 1 (MATE1/SLC47A1). It was reported that a new stop smoking aid varenicline is mainly excreted into urine and its tubular secretion is mediated by OCT2 expressed at the basolateral membrane. However, it remains unclear which transporters mediate tubular secretion of varenicline at the luminal side. In the present study, to clarify whether the renal MATE1 is one of the responsible factors of the renal clearance of varenicline, we carried out in vitro and in vivo experiments.

[Methods] HEK293 cells transiently expressing human (h) MATE1 and mouse (m) MATE1 were incubated with [14C]tetraethylammonium (TEA) with or without varenicline. Wild-type and MATE1-knockout mice were anesthetized with an intraperitoneal administration of sodium pentobarbital. Thereafter, 5 mg/kg of varenicline and 146 mg/kg of mannitol were administered via the jugular vein. A high-performance liquid chromatography was used to determine the amount of varenicline.

[Results and Discussion] [14C]TEA uptake in the HEK293 cells transiently expressing hMATE1 and mMATE1 was inhibited by the presence of varenicline in a concentration-dependent manner. The apparent IC50 values for hMATE1 and mMATE1 were 62.2±6.6µM and 255.0±37.9µM, respectively. The renal clearance and renal secretory clearance of varenicline were significantly decreased by the gene disruption of Mate1 in mice.

[Conclusions] The renal MATE1 was found to mediate tubular secretion of varenicline.

OCT2/MATE2-K DOUBLE TRANSFECTANT, AS AN IN VITRO MODEL OF RENAL HANDLING OF CATIONIC DRUGS IN HUMAN KIDNEY
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[Purpose] Human organic cation transporter 2 (hOCT2) and multidrug and toxin extrusion 1 (hMATE1) and hMATE2-K are localized at the basolateral membranes and the brush-border membranes of renal proximal tubules, respectively. In addition to MDCK-hOCT2/hMATE1 double-transfected cells (Sato T et al., Biochem Pharmacol: 76, 894, 2008; Tsuda M et al., J Pharmacol Exp Ther: 329, 185, 2009), we constructed the MDCK-hOCT2/hMATE2-K cells as another human renal epithelial model to reflect the vectorial transport of cationic compounds.

[Methods] The MDCK cells were transfected the plasmid vector containing both hOCT2 and hMATE2-K cDNA. For the transport experiments, cells were seeded on microporous membrane filters inside a Transwell® chamber with the complete medium.

[Results and Discussion] Among the 83 clones resistant against G418 treatment, the clone number 71 was selected as the double transfecant MDCK-hOCT2/hMATE2-K based on the expression of hOCT2 and hMATE2-K by RT-PCR and Western blot analysis. In transport analyses, cisplatin or oxaliplatin transport from basolateral side was observed in the MDCK-hOCT2/hMATE2-K cells. The intracellular platinum accumulations were higher from the basolateral side than those from the apical side.

[Conclusions] We successfully established the MDCK-hOCT2/hMATE2-K cells as another human renal epithelial model.