345

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THE ROLE OF ORGANIC CATION TRANSPORTERS (OCTS) FOR DRUG DISPOSITION OF TROSPIUM CHLORIDE

Hypothesis / aims of study

The muscarinic receptor antagonist trospium chloride is used for the treatment of overactive bladder (OAB). Recently, it has been shown that trospium chloride is a substrate of the multidrug carrier P-glycoprotein which highly restricts trospium chloride permeation into the brain by P-glycoprotein mediated drug efflux at the blood-brain barrier [1,2]. In contrast, carrier-mediated uptake is fairly unknown for this drug. As trospium chloride is a cationic drug it was suggested that members of the organic cation transporter family (OCTs) might be involved in trospium chloride uptake transport. OCT-mediated drug transport is of importance for drug absorption from the gut and drug excretion via bile and urine. Therefore, the aim of the present study was to examine whether trospium chloride is transported by the organic cation transporters OCT1, OCT2 and OCT3 by *in vitro* transport assays. Furthermore, drug disposition and excretion of trospium chloride was analysed in wild-type mice and *oct1/2* knockout mice, lacking the oct1 and oct2 transporters.

Study design, materials and methods

HEK293 cells were transiently transfected with cDNA constructs expression human OCT1, OCT2, or OCT3 and were used for transport assays with radiolabeled [^{3}H]trospium chloride. Furthermore, [^{3}H]trospium chloride was intravenously applied to gall bladder cannulated *oct1/2* knockout mice and wild-type mice at 1 mg/kg body weight in order to analyse *in vivo* drug disposition and hepatobiliary elimination. Drug excretion into bile and tissue concentrations were analysed over 2h.

Results

Transport studies in HEK293 cells revealed that trospium chloride was significantly transported by all human OCTs (OCT1, OCT2, and OCT3). Saturation kinetics revealed Km values of 17 µM and 8 µM for OCT1 and OCT2, respectively [3]. In agreement with these *in vitro* data, *oct1/2* knockout mice showed significantly lower hepatobiliary excretion of trospium chloride.

Interpretation of results

In the present study we demonstrate that the OAB drug trospium chloride is a transported substrate of all human OCTs. As OCTs are involved in drug transport in the gut, liver and kidney, these findings are of importance for overall drug disposition and pharmacokinetics of trospium chloride.

Concluding message

By showing trospium chloride transport by OCT carriers *in vitro* and *in vivo*, we add an important component to the understanding of drug absorption, disposition and elimination of trospium chloride in OAB patients. Furthermore, this data have to be considered for potential drug-drug interactions that might occur at the level of OCT-mediated transport of trospium chloride in the gut, liver and kidney.

References

1. 1 Geyer J, Gavrilova O & Petzinger E (2009) The role of P-glycoprotein in limiting brain penetration of the peripherally acting anticholinergic overactive bladder drug trospium chloride. Drug Metabolism and Disposition, 37:1371-1374.
2. 2 Geyer J, Gavrilova O & Schwantes U (2010) Differences in the brain penetration of the anticholinergic drugs trospium chloride and oxybutynin. UroToday International Journal, doi:10.3834/uiju.1944.5784.2010.02.12.
3. 3 Wenge B, Geyer J & Bönisch H (2010) The anticholinergic drugs oxybutynin and trospium chloride are substrates of the human organic cation transporters. Naunyn-Schmiedeberg's Archives of Pharmacology, 383:203-208.

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Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**

Name of ethics committee	**Regierungspräsidium Gießen** **Dezernat V 54 - Veterinärwesen** **(Hessian Ethical Committee)**