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CARRIER-MEDIATED ACCUMULATION AND RELEASE OF TROSPIUM CHLORIDE IN IMMORTALIZED HUMAN UROTHELIAL UROTSA CELLS

Hypothesis / aims of study

The anticholinergic drug trospium chloride, which is used for treatment of overactive bladder (OAB), is mainly excreted via urine in its active form. Within the urinary bladder trospium chloride has local anticholinergic effects, which contribute to its clinical properties. However, depending on the dosing and application regime, the urinary drug concentration can be highly variable. In the present study we asked if at high urinary concentrations trospium chloride can accumulate in the cells of the urothelium and again can be released when the urinary drug concentration declines. As trospium chloride is a highly hydrophilic drug, cellular uptake and release would require carrier-mediated transport via e.g. organic cation transporters (OCTs) or multidrug resistance (MDR1) P-glycoprotein, which previously showed transport of trospium chloride across membranes [1,2].

Study design, materials and methods

Accumulation and release of [^{3}H]trospium chloride was analyzed in immortalized human urothelial UROtsa cells as an *in vitro* model of the human bladder urothelium [3]. As drug transporters were supposed to be involved in this process, we also screened for carrier expression in UROtsa cells by real-time PCR.

Results

UROtsa cells showed expression of the muscarinic receptors M1-M5 (with the highest expression of M3) and of carnitine acetyltransferase CarAT. In contrast, expression of choline acetlytransferase (ChAT) and vesicular acetylcholine transporter (VAChT) were undetectable. Furthermore, UROtsa cells express the trospium chloride transporters OCT1 and MDR1. UROtsa cells showed a significant time-dependent accumulation of 10 µM [^{3}H]trospium chloride. Following accumulation, the cells even released the drug in a time-dependent manner.

Interpretation of results

It seems that [^{3}H]trospium chloride can accumulate in the urothelium by carrier-mediated uptake, when drug concentrations are high. At low extracellular drug concentrations [^{3}H]trospium chloride then can be released.

Concluding message

By the accumulation of trospium chloride the urothelium may build a local depot whenever urinary drug excretion is high. At low urinary drug concentrations trospium chloride may be released again and so may maintain a more constant local trospium chloride concentration at the urothelium even when the urinary concentration declines.

References

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