Regulation of Human Renal Drug Transporter mRNA Expression by Proinflammatory Cytokines

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Proinflammatory cytokines, which are elevated during inflammation or infections, can affect drug pharmacokinetics (PK) and pharmacodynamics in humans due to altered expression or activity of drug transporters and/or metabolizing enzymes. To date, studies have examined the effect of cytokines on the activity and/or expression of hepatic transporters and drug-metabolizing enzymes. However, many antibiotics and antivirals used to treat infections are renally cleared by transporters including the basal organic cation transporter 2 (OCT2), organic anion transporters 1 and 3 (OAT1 and 3), and the apical multidrug and toxin extrusion proteins 1 and 2-K (MATE1/2-K). Therefore, the goal of this study was to determine the effect of individual and cocktail of the major cytokines, interleukin-6 (IL-6), IL-1β, tumor necrosis factor (TNF)-α, and interferon-g (IFN-g) on the mRNA expression of human renal transporters using primary human renal proximal tubular epithelial cells (PTECs). Renal cortical tissue, excised from whole human kidneys, was subjected to enzymatic digestion, and the PTECs were isolated by density centrifugation with Percoll. Adhered PTECs on collagen-coated plates were then treated for 72 hours with the above individual or combined cytokines at concentrations of 0.1, 1, and 10 ng/mL in triplicate with daily medium change, and the experiments were conducted in PTECs isolated from 2 female, premenopausal donors. Total RNA was then isolated and subjected to qPCR analysis for multiple renal transporter genes. Exposure to the cytokine cocktail for 72 hours was found to significantly downregulate mRNA expression (in a concentration-dependent manner) of OCT2 and the organic anion transporting polypeptides 4C1 (OATP4C1), by up to 60% and 80%, respectively. An interesting trend was observed with OAT1 and 3, where their mRNA expression was first downregulated at the low cytokine concentration (0.1 ng/mL) and then increased as the cytokine concentration increased. The mRNA expression of the apical transporters, namely MATE2-K, the multidrug resistance protein 2 (MRP2), OAT4, and P-glycoprotein (P-gp), was also significantly downregulated in a concentration-dependent manner by up to 68%, 67%, 75%, and 63%, respectively. Interestingly, the mRNA expression of the novel organic cation transporter 1 (OCTN1) and MRP3 was induced in a concentration-dependent manner by up to 4- and 2.3-fold, respectively. In addition, although the effect elicited by the individual cytokines was less potent, the trend was similar as for the cytokine cocktail, except that the cytokine cocktail appeared to have a synergistic effect in regulating the transporter genes. Furthermore, the data obtained from both donors were comparable. Together, our results show that IL-6, IL-1β, TNF-α, and IFN-g likely synergistically regulate the mRNA expression of various renal uptake and efflux transporters in human PTECs. These changes could potentially translate into changes in protein abundance or activity of these transporters (our future studies), and thus alter drug PK during inflammation or infections.

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