Apical Shear Stress Enhances Organic Cation Transport in hOCT2/hMATE1 Transfected MDCK Cells

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Background:

Active transport by renal proximal tubules plays a significant role in human drug disposition and is therefore important to model when developing drugs. However, current *in vitro* drug testing methods fail to mimic important physiological cues, such as flow induced shear stress. In this study, the effect of shear stress on active transport was investigated using a parallel plate bioreactor cultured with MDCK cells expressing human organic cation transporters.

Methods:

A polycarbonate parallel plate bioreactor compatible with Snapwell inserts was used in these experiments (Fig. 1). The device provides a flow path across the apical side of the cells and a static media reservoir on the basal side. MDCK cells transfected with a pair of uptake and efflux transporters (hOCT2/hMATE1) were grown on Snapwells under static conditions until confluence and then placed in the bioreactor. Media flow was increased over 7 days until shear stress of 0.2 dynes/cm^2 was achieved. Uptake of 25μM 4-(4-dimethylamino)styryl-N-methylpyridinium (ASP+), a fluorescent OCT2/MATE1 substrate, was measured for 1 hour with or without pretreatment (30 minutes) with 500μM imipramine, an OCT2/MATE1 inhibitor. Control cells were cultured under static conditions.

Results:

Cells maintained under flow showed a 2.2 fold increase in protein concentration over static controls, confirming previous observations of shear stress effects. Furthermore, cells cultured under shear stress showed a 2.4 fold increase in ASP+ uptake when compared to cells cultured under static conditions and a 63.4±3.7% inhibition with imipramine compared to 48.6±5.5% inhibition in static cells (Fig. 2).

Conclusions:

These results indicate that exposure to shear stress increases uptake of the active transport substrate ASP+ compared to static growth conditions.