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/cm² 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.