PULMONARY ABSORPTION OF IPRATROPIUM VIA TRANSPORTERS IN CULTURED HUMAN BRONCHIAL EPITHELIAL CELLS
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[Purpose] Ipratropium bromide (Ipra) is an anticholinergic drug used for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Despite of low oral bioavailability of Ipra, superior systemic exposure is achieved on inhaled dosing. Therefore, we investigated the pulmonary absorption mechanism of Ipra using human bronchial epithelial cell-derived BEAS-2B cells. [Method] [3H]Ipra was used to assess the uptake activity by the cell line. Contribution of OCTN1/2 to Ipra uptake was evaluated by measuring [3H]Ipra uptake by BEAS-2B expressing shRNA to OCTN1 or OCTN2. [Result and Discussion] Uptake of [3H]Ipra by BEAS-2B cells was significantly higher at 37ºC than at 4ºC. Uptake of Ipra by BEAS-2B cells was saturable with $K_m$ of 78 µM, suggesting Ipra uptake was mediated by transporters expressed in this cell line. Since Ipra is a cation, expression of organic cation transporters were studied in BEAS-2B cells by RT-PCR. RT-PCR showed that OCTN1 and OCTN2, but not any OCTs, were expressed in BEAS-2B cells. Uptake of [3H]Ipra by HEK293 cells expressing OCTN1 or OCTN2 was significantly increased compared with mock-transfected cells and the estimated $K_m$ values were 444 µM and 32 µM, respectively. When OCTN1 or OCTN2 was knocked-down in BEAS-2B cells, uptake of [3H]Ipra was suppressed to 78 % and 15% of its uptake by cells expressing shRNA not related to OCTN genes, respectively. [Conclusion] It was demonstrated that Ipra could be taken up by the bronchial epithelial cells by transporters including OCTN1 and OCTN2.