DECREASED DISTRIBUTION OF AN ORGANIC CATION, TRIETHYLMETHYLAMMONIUM TO THE KIDNEY IN RATS WITH URANYL NITRATE-INDUCED ACUTE RENAL FAILURE IN ASSOCIATION WITH rOCT2-SPECIFIC IMPAIRMENT

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To estimate the effect of uranyl nitrate (UN) – induced acute renal failure (ARF) on the tissue distribution of organic cations (OCs), different doses (0.3, 3, 9, 15 and 30 μmole/kg rat) of [3H]-triethylmethylammonium (TEMA) were administered intravenously to control and UN-ARF rats, and the plasma concentration and ratio of tissue-to-plasma concentrations (T/P) in various organs were examined. In UN-ARF rats, the AUC was increased significantly compared to control rats. Interestingly, with increasing dose of TEMA, the AUC increased linearly in control rats, but increased superlinearly in UN-ARF rats. As a result, the CLs decreased significantly in the case of UN-ARF at high TEMA doses (i.e., 15 and 30 μmole/kg). The T/P ratio of TEMA was not changed by UN-ARF for the liver, brain, heart, lung, spleen and small intestine. However, the T/P ratio for the kidney was decreased significantly in UN-ARF rats with increasing dose of TEMA (e.g., from 43.5 to 8.2 for a 3 μmole/kg dose vs. 53.5 to 8.1 for a 30 μmole/kg dose). In UN-ARF, the expression of mRNA in the kidney for rOCT2, but not for rOCT1, was significantly decreased. No change for rOCT1 and rOCT2 (absent) in the liver was observed. Above results suggest that the kidney-specific decrease in the distribution of TEMA (i.e., T/P) in rats by UN-ARF is associated with renal rOCT2-specific impairment.

Keywords: TEMA, Acute renal failure, Pharmacokinetics, Tissue distribution, RT-PCR, Organic cation.

THE ESTABLISHMENT OF IN VITRO AIRWAY DRUG DELIVERY MODEL USING AIR-LIQUID INTERFACE (ALI) STATE OF HUMAN BRONCHIAL EPITHELIAL CELL MONOLAYERS

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The purposes of this study were to establish the air-liquid interface (ALI) culture of human bronchial cell monolayer and to survey the transepithelial permeability of a series of anti-allergic drugs. Human normal bronchial epithelial (NHBE) cells were plated on Transwell® following an air-liquid interface culture from day 3, which resulted in a peak TEER value on the 8th day. Morphological characterization was observed and the formation of tight junctions was verified by actin staining. The Papp of P-gp substrate (5 μM rhodamine123) in apical to basolateral direction was lower than that of the reverse direction, which indicated the expression of P-gp transporter. The expression of MDR1 mRNA was also demonstrated by RT-PCR assay. The transepithelial permeability of human bronchial epithelial monolayer was performed using albuterol hemisulfate, albuterol, fexofenadineHCl, dexamethasone, triamcinolone acetonide and budesonide. Through the comparison between Papp value of the most hydrophilic compound (albuterol hemisulfate) and Papp value of highly lipophilic compound (Budesonide), the fact that the Papp value significantly increased with the increase of lipophilicity of the compound is identified. Moreover, a linear relationship of Papp was obtained between the ALI human bronchial monolayer and liquid-covered human nasal monolayer, which implies that simple passive diffusion is the predominant pathway of the transepithelial transport of anti-allergic drugs. Thus, the in vitro human bronchial cell monolayers seem to provide a promising and convenient method for respiratory drug transport evaluation.