2-P-75

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS OF JHL45, A NOVEL IMMUNE MODULATOR RELATED ATOPIC DERMATITIS, IN NC/Nga MICE

In-hwan Baek, MS1, Jung-woo Chae, BS1, Chu-young Son, BS1, Kwang-il Kwon1*, PhD
1College of Pharmacy, Chungnam National University, Daejeon, 305-764, South Korea

JHL45 was synthesized from decursin isolated from Angelica gigas and expected to be an effective agent in treating and preventing atopic dermatitis in previous study. In this study, the dose dependent pharmacokinetics and pharmacodynamic analysis of JHL45 was developed using NC-Nga mice, the animal model for atopic dermatitis, after oral administration of 1 mg/kg, 3 mg/kg, 10 mg/kg, respectively. Atopic dermatitis of NC/Nga mouse was induced by 1-chloro 2,4-dinitrobenzene (DNCB) contact for 5 weeks, and dexamethasone was used as a positive control for the comparison of anti atopic dermatitis effect of JHL45. The plasma concentration of JHL45 was determined using HPLC-MS/MS (API 2000), and the pharmacodynamic parameters of immunoglobulin E (IgE), interleukin-4 (IL-4), IL-5, IL-6, IL-13 were analyzed using ELISA. The mean value of the maximum plasma concentration (C_{max}) of JHL45 and the time of C_{max} (T_{max}) are 0.05 ± 0.08 μg/ml x kg and 0.19 ± 0.24 hr for JHL45 1 mg/kg group, 0.05 ± 0.06 μg/ml x kg and 0.29 ± 0.53 hr for JHL45 3 mg/kg group, 0.08 ± 0.11 μg/ml x kg and 0.11 ± 0.17 hr for JHL45 10 mg/kg group, respectively. A parent-metabolite compartment model with delay parameter between parent and metabolite compartment described the pharmacokinetics of JHL45 and its metabolite with double peak phenomenon. IgE concentration in serum was significantly inhibited dose dependently compared with control group (non-treated). The expression of IL-4, IL-5, IL-6, IL-13 in spleen cell were significantly inhibited compared with those of control group (non-treated), and it was comparable to positive control (dexamethasone group). This study will be useful for further pharmacokinetic and pharmacodynamic studies of JHL45 during preclinical and clinical trials.

Key words: JHL45, (+)-decursinol, atopic dermatitis, pharmacokinetics, pharmacodynamics

2-P-76

ROSIGLITAZONE, A PPAR γ AGONIST, STIMULATES PARACELLULAR TRANSPORT IN PRIMARY COLLECTING DUCT CELLS.

Sunhapas Soodvilai1, Zhanjun Jia2, and Tianxin Yang2
1Department of Physiology, Faculty of Sciences, Mahidol University, Bangkok, Thailand. 2Department of Internal Medicine, University of Utah and Veterans Affairs Medical Center, Salt Lake City, Utah, the United States

[Purpose] The involvement of peroxisome proliferator-activated receptor gamma (PPARγ) in mediating thiazolidinedione-induced fluid retention has been reported. However, the mechanism of increased fluid reabsorption in the distal nephron in response to PPARγ agonist is still controversial.

[Methods] We determined the mechanisms of rosiglitazone (RGZ)-stimulated ion transport using the electrophysiological studies on primary cultures of inner medullary collecting duct (IMCD) cells.

[Result and Discussion] Exposure IMCD cells monolayers to RGZ, amiloride-sensitive short-circuit current (Isc), an index of ENaC activity, was unchanged at 24 h but was significantly decreased at 48 h, corresponding to parallel inhibition of mRNA expressions of α-, β-, and γ-ENaC. Despite ENaC inhibition, the transepithelial resistance (TER) and transepithelial voltage (Vt) were significantly reduced after treated with RGZ, suggesting that an alternative route contributed for an increased of ion transport. Therefore, we examined whether RGZ affected on paracellular Na⁺ and Cl⁻ transport. RGZ treated IMCD cells monolayers exhibited increases of the paracellular Cl⁻ transport, to less extent, the paracellular Na⁺ transport.

[Conclusion] Our data suggest that PPARγ activation by PPARγ agonist stimulated paracellular ion transport and inhibited ENaC in primary IMCD cells.