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The stabilizing effect of dipeptidyl peptidase-4 inhibitors on the epithelial barrier in the colistin-induced tubular injury

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Objectives:

Recently, dipeptidyl peptidase-4 inhibitors (DPP4i) have been identified to have some pleiotropic effects in different kidney diseases including diabetic kidney disease, ischemic acute kidney injury. In terms of pathophysiology, few studies have examined the effects of DPP4i on the epithelial barrier in drug-induced acute kidney injury. The increased tubular epithelial cell permeability and barrier dysfunction have been shown in previous studies regarding colistin-induced nephrotoxicity. This study was performed to evaluate the renoprotective effect of DPP4i in colistin-induced tubular injury using a two-layered kidney-on-a-chip device.

Methods:

The kidney-on-a-chip device consists of upper and lower channels mimicking intraluminal space and interstitial space. Kidney tubular epithelial cells were seeded into upper channel and exposed to colistin at a concentration of 400 µg/ml for 48 hours under physiological shear stress condition (1 dyn/cm²). Evogliptin (Suganon®, Dong Ah Pharm., Korea) was administered to the lower channel at a concentration of 50 nM for 48 hours. Transmembrane permeability, tight junction protein expression, cell viability, and tubular injury marker, kidney injury molecule-1 (KIM-1), in outlet-collected media were evaluated in evogliptin-treated and control groups.

Results:

After colistin treatment, transmembrane permeability increased from 6.75% to 51.5%, but evogliptin decreased transmembrane permeability to 34.6%. In addition, the fluorescence intensity of tight junction proteins, occludin and ZO-1, which were reduced by 56.2% and 44.5% after colistin exposure, were maintained during the treatment with evogliptin. The dead cell percentage and KIM-1 level were slightly decreased in evogliptin-treated groups.

Conclusions:

We identified some renoprotective effects of the DPP4i on the epithelial barriers in short-term colistin-induced tubular injury. Further studies are required for the cytoprotective effect in long-term colistin injury models.

Figure 1. Confocal fluorescent images of tight junction protein Occludin and ZO-1 expression in negative control, colistin-only exposure, colistin and evogliptin exposure groups

