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Clarification of Regulatory Mechanism of Salt Balance through Intercellular Tight Junction by Kidney-Gut Interaction

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Summary

The absorption (reabsorption) of Na^+ and Cl^- in the intestine and kidney is controlled by renin-angiotensin-aldosterone (RAA) system, but the mechanisms are not fully understood. In mice fed with NaCl-depleted diets, the expression levels of claudin-2 and -7, tight junctional proteins, increase compared to those in control mice. Claudin-2 expression is upregulated by ALD, but the regulatory mechanism of claudin-7 has not been clarified. Here, we found that angiotensin II (ANGII) increases claudin-7 expression mediated by the activation of NF-kB pathway in mouse colonic MCE301 cells. Dilution potential assay indicated that ALD may inhibit Na^+ secretion mediated by the reduction of claudin-2 expression and ANGII may promote Cl^- absorption mediated by the elevation of claudin-7 expression. Furthermore, the expressions of claudin-2 and -7 may be inversely regulated by a complex of p53 and HNF4a in the colon crypt.

Expression linkage between claudins and ion transporters expressed in the plasma membrane were investigated using MCE301 cells. ALD decreased the mRNA levels of Na^+/H^+-exchanger 2 (NHE2) and NHE3, which were inhibited by claudin-2 siRNA. Furthermore, the expression levels of NHE2 and NHE3 were decreased by the overexpression of claudin-2. These results suggest that the expressions of NHE2 and NHE3 are controlled by claudin-2 in the colon.

In the collecting duct of mice fed with NaCl-depleted diets, the expression levels of claudin-3 and -8 were upregulated and downregulated, respectively. ALD increased the mRNA level of claudin-3 in mouse collecting duct-derived mIMCD-3 cells, which was inhibited by spironolactone, a mineralocorticoid receptor antagonist. In addition, the permeability of Na^+ was decreased by aldosterone, which was inhibited by spironolactone and claudin-3 knockdown. These results suggest that ALD may inhibit the secretion of Na^+ mediated by the elevation of claudin-3, resulting to promote salt reabsorption in the kidney.

In the present study, we found that the expression levels of claudin-2 and -7 in the colon and claudin-3 and -8 in the collecting duct are controlled by the RAA system. In addition, the expressions of NHE2 and NHE3 were downregulated by claudin-2 in the colon, suggesting that claudins are involved in the regulation of not only paracellular ion transport, but also transcellular ion transport. We suggest that the homeostasis of salt balance is cooperatively regulated by claudins and ion transporters in the plasma membrane in the colon and kidney.