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Effects of Aging and Magnesium Metabolism Disorder on Paracellular NaCl Transport in Intestines

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Summary

Intracellular Mg^{2+} functions as a cofactor for ATP-dependent enzymes and plays an important role in the control of physiological homeostasis. Hypertension, diabetes, and chronic kidney disease may be worsened by Mg^{2+} deficiency. However, the effect of Mg^{2+} deficiency on geriatric diseases is largely unknown. NaCl was previously thought to be absorbed via various ion channels and transporters in the plasma membrane of intestinal epithelial cells. Recently, the involvement of claudins (CLDNs), which are components of tight junctions (TJs), has been clarified. CLDNs contains subtypes over 20 and the function of TJs are controlled by the combination of each CLDNs. Here, we investigated the effect of aging and Mg^{2+} deficiency on the expression and function of CLDNs.

So far, we found that the colonic expression levels of CLDN3, 7, 15 in aged mice are higher than those in young mice. Mg^{2+} deficiency induced the elevation of CLDN3, 7, and 15 expression in the mouse colon-derived MCE301 cells. In addition, ATP level was reduced by Mg^{2+} deficiency. The reduction of ATP content induces the activation of AMP-activated protein kinase (AMPK)/ mammalian target of rapamycin (mTOR) pathway. The elevation of CLDN3, 7, and 15 expression was inhibited by an AMPK inhibitor, but not by a mTOR activator. These results indicate that other downstream factors may be involved in the upregulation of these CLDNs. In the immunofluorescence assay, CLDN7 was localized at the TJs under normal conditions, whereas both CLDN3 and CLDN15 were mainly distributed in the cytosol. The fluorescence signals of these CLDNs were enhanced by Mg^{2+} deficiency, but the localization was unchanged. Transepithelial electrical resistance (TER) was decreased by Mg^{2+} deficiency, which was partially inhibited by CLDN7 silencing. In contrast, TER was decreased by CLDN7 overexpression. In a dilution assay, the ratio of permeability of Cl^- to Na^+ was unchanged by Mg^{2+} deficiency, but that was reduced by CLDN7 silencing. Our data indicate that NaCl permeability may be enhanced with aging mediated via the change of some CLDNs expression.