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# Search for Chemical Chaperon and Associated Protein which Improve the Mislocalization of Claudin-16 Magnesium Channel

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Summary

The magnesium balance of whole body is regulated by the kidney which adapts $Mg^{2+}$ excretion based on net $Mg^{2+}$ absorption from the intestine. $Mg^{2+}$ filtrated by glomeruli is reabsorbed by transcellular and paracellular pathways in renal tubular epithelial cells. Claudin-16 (CLDN16) regulates the paracellular reabsorption of $Mg^{2+}$ in the thick ascending limb (TAL) of Henle's loop. Genetic disorders of CLDN16 cause mislocalization of CLDN16, resulting in hypomagnesemia. There is no effective treatment for hypomagnesemia except for magnesium administration. Here, we searched for a novel drug to restore tight junctional localization of a CLDN16 mutant. A D97S mutant, which has a mutation in the first extracellular loop (ECL) of CLDN16, was mainly colocalized with endosome marker, whereas wild-type (WT) CLDN16 was colocalized with ZO-1, an adaptor protein of tight junctions. The protein stability of the D97S mutant was lower than that of the WT. The expression level of the D97S mutant was increased by lactacystin, a proteasomal inhibitor. Endocytosis inhibitors increased the tight junctional localization of the D97S mutant. We found that primaquine, an antimalarial agent, increased the protein stability and cell surface localization of the D97S mutant, but the localization of other mutants, which have mutations in the cytosolic domain or second ECL, was not affected. Paracellular $Mg^{2+}$ flux was increased by primaquine in D97S mutant-expressing cells. These results suggested that primaquine increases the tight junctional localization of the D97S mutant, resulting in an elevation of $Mg^{2+}$ reabsorption. Primaquine may become an effective treatment drug for selected patients with mutant CLDN16.