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Mechanisms of hypertension caused by mutations of WNK kinases, novel regulators of NaCl handling in the kidney

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Summary

Pseudohypoaldosrteronism typell (PHAII), known as Gordon syndrome, is an autosomal dominant disorder characterized by hypertention, hyperkalemia, and hyperchloremic metabolic acidosis. Recently, positional cloning linked mutations in two homologous protein kinase genes, WNKl and WNK4 to PHAII.

WNKs [With No Lysine (K)] kinases are recently discovered serine-threonine protein kinases that may play an essential role in the regulation of electrolyte homeostasis. PHA II-causing mutations in the WNKl gene are large deletions in the first intron that appears to increase WNKl mRNA expression. On the other hand, mutations in the WNK4 gene are missense mutations that cluster within a span of four amino acids distal to the first putative coil domain.

We have previously reported that a disease-causing mutant WNK4 increased paracellular chloride permeability and claudin phosphorylation in MDCK II cells.

The purpose of this study was to determine whether the increased WNKl expression had the same effect on paracellular chloride permeability and claudin phosphorylation as the disease-causing WNK4 has.

After generating WNKl-expressing cell lines in MDCKII cells, we measured paracellular chloride permeability and claudin phosphorylation, and found that both were significantly increased by WNKl overexpression. This suggested that increased chloride shunt induced by WNKl overexpression or missense mutations of WNK4 might cause PHAII. Further analysis using WNKl transgenic mice or WNK4 knock-in mice may be necessary for identification of true pathogenesis of this disease.