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RENAL PHYSIOLOGY

Aldosterone-dependent NCC activation

A new study has identified a mechanism linking aldosterone to activation of the NaCl cotransporter (NCC), which has important roles in renal sodium reabsorption and blood-pressure homeostasis. "Aldosterone is a potent NCC activator, but the mechanism by which it interfaces with the WNK kinase pathway to trigger NCC phosphorylation and activation had not been defined," explains researcher Arohan Subramanya.

When analysing the sequence of WNK1 kinase, Subramanya and colleagues noticed binding sites for the ubiquitin ligase NEDD4-2 in an proline-rich region that undergoes alternative splicing. They found that WNK1 isoforms containing these binding sites were highly expressed in human distal nephrons and were targeted for proteasomal degradation by NEDD4-2. "As NEDD4-2 can be blocked by the aldosterone-induced kinase SGK1, this finding suggested a mechanism by which aldosterone could increase WNK1 levels, resulting in increased WNK signalling and phosphorylation of NCC," says Subramanya.

Further investigations in cell culture models demonstrated that WNK1 acts downstream of NEDD4-2 and SGK1 to modulate NCC activity, suggesting an essential role of WNK1 in the aldosterone response. Consistent with these data, aldosterone infusion increased the levels of proline-rich Wnk1 isoforms in wild type mice, but not in *Nedd4-2* knockout mice, which had high Wnk1 expression and NCC activity at baseline.

"Our data suggest that alterations in WNK-dependent signalling contribute to the pathogenesis of diseases of aldosterone excess, and add to the emerging paradigm that drugs that block WNK kinases could be used to treat a variety of common conditions, such as hypertension and congestive heart failure," concludes Subramanya.

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Original article Roy, A. *et al*. Alternatively spliced proline-rich cassettes link WNK1 to aldosterone action. *J. Clin. Invest*. doi:10.1172/JCI75245