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Mice lacking p300/CBP-associated factor have a resistance to salt-induced hypertension probably through dysregulation of NKCC2 and aquaporin 2

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Objectives: p300/CBP-associated factor (PCAF), a member of the GNAT acetyltransferase family, is involved in the modulation of differentiation and cell cycle progression. Several neurodegenerative conditions have been thought to be associated with an alteration of PCAF activity and subsequent histone acetylation, and patients with neurodegenerative diseases often experience hypotension although the consequence of dysfunctional PCAF on blood pressure remains unknown. This study investigated a potential role of PCAF in the relationship between blood pressure and urinary sodium and water excretion in the kidney.

Methods: PCAF knockout (KO) mice and wild-type (WT) mice received 8% or normal NaCl salt diet for 2 weeks.

Results: WT mice had higher blood pressure on a high-salt diet than on a normal salt diet, but changes of dietary salt did not affect the blood pressure of PCAF KO mice. Free water clearance (FWC) and electrolyte free water clearance (EFWC) in PCAF KO mice on a high-salt diet were higher than those of WT mice on a high-salt diet. Both PCAF KO and WT mice on a high-salt diet had higher expression of Na⁺/H⁺ exchanger isoform 3 (NHE3) compared with normal salt-fed groups. In PCAF KO mice fed a high-salt diet, there was an increase in renal expression of Na⁺-Cl⁻ cotransporter (NCC) and a decrease in renal expression of Na⁺-K⁺-2Cl⁻ cotransporter (NKCC2) compared with WT mice fed a high-salt diet. Although renal mRNA expression of aquaporin 2 (AQP2) was upregulated in all groups on a high-salt diet, the phosphorylated protein level of AQP2 at serine 261 was significantly increased only in PCAF KO mice on a high-salt diet.

Conclusions: A deletion in PCAF expression makes blood pressure less sensitive to salt probably via inappropriate downregulation of NKCC2 and AQP2 in kidneys, indicating that genetically impaired PCAF activity is likely to affect how blood pressure responds to changes in dietary salt.