Overexpression of a HIF-4-prolyl hydroxylase Transgene in the Renal Medulla

Increases the Salt Sensitivity of Arterial Blood Pressure

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Abstract

We have demonstrated that HIF-4-prolyl hydroxylase domain-containing proteins (PHDs), a family of enzymes that promote HIF-1α degradation, are abundantly present in the renal medulla and regulate sodium excretion through regulation of HIF-1α and its target genes, such as nitric oxide synthase, cyclooxygenase and heme oxygenase. The present study was designed to test the hypothesis that overexpression of PHD2 transgene in the renal medulla increases the salt sensitivity of blood pressure. Phakoid expressing PHD2, the predominant isoform of PHDs in the kidneys, were transferred into the renal medulla in uninephrectomized rats. Three weeks after PHD2 transfection, the mRNA levels of PHD2 were increased by two folds in the renal medulla. Mean arterial pressure measured by a telemetry system was significantly raised in PHD2 transplanted rats after high salt challenge compared with control animals (131.3 ± 6.7 vs. 110.7 ± 4.2 mmHg). There was no blood pressure change in PHD2 transplanted rats that were maintained on the normal salt diet. Urinary sodium excretion in response to acute sodium loading or elevation of renal perfusion pressure were blunted by 30% and 50%, respectively, in PHD2 transplanted animals. In conclusion, PHD2 in the renal medulla importantly participates in the regulation of renal medullary functions and is the long-term control of arterial blood pressure.

Method

RESULTS

A: Figure 1. Overexpression of PHD2 transgene increased PHD2 mRNA levels and decreased HIF-1α protein levels in the renal medulla. A: The animals transfected with PHD2 plasmid, the PHD2 levels were increased by two folds compared with that in control animals. Although high salt (HS) intake significantly suppressed the expression of PHD2, the levels of PHD2 in PHD2-transfected animals were preserved after high salt diet for 3 weeks and the same level in control animals on a low salt diet. These results demonstrated a successful PHD2 gene transfection that preserved the decrease in PHD2 levels in the renal medulla after high salt intake. * P < 0.05 vs. low salt diet (LS) from control rats or PHD2 rats, respectively. # P < 0.05 vs. control on the same salt diet n = 6. B: PHD2 transfection reduced HIF-1α levels in the renal medulla (low salt diet, n = 3).

B: Figure 2. Effect of renal medullary PHD2 transfection on pressure natriuresis. We compared diuretic and natriuretic responses to the elevation of renal perfusion pressure (RPP) between control animals and PHD2 transplanted animals. Both the urine flow and urinary sodium excretion rates were remarkably increased in response to the elevation of RPP. These pressure diuretic and natriuretic responses were significantly blunted in PHD2 plasmid transplanted group compared with the control group. These data indicate that overexpression of PHD2 impaired renal medullary function. * P < 0.05 vs. PHD2 rats, (n = 5).

Figure 3. Effects of renal medullary PHD2 transfection on urinary sodium excretion in response to acute sodium loading. To further evaluate the impact of renal medullary PHD2 transfection on renal sodium handling, we examined the sodium excretion after acute sodium loading. Acute sodium loading dramatically increased urine volume (UV) and urinary sodium excretion (UVNa). These increases in UV and UVNa were considerably attenuated in PHD2-treated rats. These results demonstrated that overexpression of PHD2 transgene in the renal medulla remarkably impaired the capability of the kidneys to remove extra sodium load. These data additionally suggest that renal medullary PHD2 is a crucial determinant in the regulation of sodium excretion. * indicates P < 0.05 vs. PHD2 rats (n = 5).

SUMMARY

> Overexpression of PHD2 transgene prevented high salt-induced suppression of PHD2 in the renal medulla.
> Overexpression of PHD2 transgene decreased HIF-1α levels in the renal medulla.
> Overexpression of PHD2 transgene in the renal medulla increased salt sensitivity of blood pressure.

CONCLUSION

Renal medullary PHD senses the high salt intake and mediates renal salt adaptation, thereby, regulates salt sensitivity of blood pressure.