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Aldosterone Blockade Induces Hypoxia in the Neonatal Rat Kidney

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Hypoxia is regarded as an important physiological factor to control nephrogenesis, which is accompanied by the growth and development of the renal vascular system. We have demonstrated that aldosterone blockade impairs cell proliferation, apoptosis, and mitogen- activated protein kinase family expressions in the neonatal rat kidney. Notably, decreased plasma aldosterone levels have been demonstrated in a number of various hypoxic models in vivo. In this study, we hypothesized that aldosterone inhibition in developing kidney affects hypoxia- related target genes important for renal vasculogenesis. Newborn rat pups were treated with spironolactone (200 mg/kg/d) in olive oil or olive oil for 7 d. Tissue hypoxia was assessed by uptake of a hypoxic probe, pimonidazole (200 mg/kg), and expression of hypoxia- responsive genes. Immunoblot, RT- PCR and immunohistochemistry (IHC) for the expression of hypoxia- inducible factor (HIF)- 1α , HIF- 2α , Ets- 1, vascular endothelial growth factor (VEGF), and heme oxygenase (HO)- 1 were performed. In the spironolactone- treated group, HIF- 1α , Ets- 1 and HO- 1 protein expressions were significantly increased ($P < 0.05$), whereas VEGF and HIF- 2α protein expressions were not changed, compared with the control group. RT- PCR showed no differences between the two groups. IHC stain showed increased expressions of HIF- 1α , Ets- 1, VEGF, and HO- 1 by spironolactone treatment. Especially, HIF- 1α , Ets- 1, and VEGF expresssions were highly activated in medullary and cortical collecting ducts, tubules, and glomeruli. HO- 1 expression was strongly detected in proximal & collecting tubular cells and glomeruli in cortex and corticomedullary junction. Pimonidazole staining showed that many collecting ducts, developing & maturing tubules and glomeruli in cortex and medulla undergo severe hypoxia by spironolactone treatment. In summary, these data show that aldosterone inhibition in the developing rat kidney induces hypoxic response, and up- regulates the expressions of key mediators of hypoxia including HIF- 1α , Ets- 1, VEGF, and HO- 1.

Key Words : 알도스테론, 저산소증, 신발생
Aldosterone, Hypoxia, Nephrogenesis