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Role of arginase II in renal water reabsorption and obesity-induced renal damage

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Arginase II (Arg-II) is one of the two isozymes (Arg-I and Arg-II) and abundantly expressed in the kidney. Arg-II catalyzes hydrolysis of L-arginine to L-ornithine and urea and thus competes with NOS for the common substrate L-arginine. Recent studies have reported Arg-II mediates diabetic renal injury and represents an important mechanism in inducing eNOS uncoupling leading to oxidative stress and vascular inflammatory responses. However, the pathophysiological role of Arg-II in the kidney is still elusive.

Kidneys play a critical role in maintaining the constancy of composition of the body's internal fluid environment. The human body controls blood volume and osmolality by AVP-dependent trafficking of water channel AQP2 to the apical membrane of the collecting duct principal cells. Although the role of AVP-cAMP-PKA signaling pathway in AQP2 shuttling is widely accepted, the mediators involved in the process are largely unknown.

Our first study demonstrates that Arg-II negatively regulates AQP2 and urine concentrating capability in kidney through inhibition of p38-MAPK. In Arg-II-deficient mice (Arg-II$^{-/-}$), total and membrane-associated AQP2 protein levels are significantly higher as compared to wild type (WT) controls. Water deprivation enhances Arg-II expression, AQP2 levels and membrane association in collecting ducts. These effects of water deprivation on AQP2 are stronger in Arg-II$^{-/-}$ than WT mice. Urine concentrating capability is more pronounced in Arg-II$^{-/-}$ mice as reflected by less urine volume and higher urine osmolality under water deprivation, which correlates with weaker increase in plasma osmolality in Arg-II$^{-/-}$ mice. Plasma vasopressin level displays no difference under water deprivation between both genotypes of mice. The effect of Arg-II can be blocked by inhibition of p38-MAPK and silencing Arg-II does not cAMP levels.

Obesity has been identified as an independent risk factor for chronic kidney disease. Although the detrimental effect of obesity on kidney has been recognized for decades, the mechanisms involved in obesity-related renal diseases are complicated and not well understood.

In the second study, we demonstrate that Arg-II deficiency in mouse protects against obesity-associated renal alterations. In WT mice, HFD feeding causes frequent renal lipid accumulation, enhancement of renal ROS levels which could be attenuated by a NOS inhibitor, suggesting uncoupling of NOS in kidney. HFD feeding also significantly augments renal Arg-II expression and activity. All the alterations in the kidney under HFD feeding are reduced by Arg-II deficiency. In addition, HFD-induced increases in mesangial matrix expansion and renal expression of adhesion molecules (VCAM-1and ICAM-1) are reduced in Arg-II$^{-/-}$ mice.

Jury:

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