Renal Sodium Handling and Hypertension

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Renal sodium handling is known as an important function that maintains both body fluid volume and blood pressure regulation. Recently, advances in molecular biology have led that alterations of tubular sodium handling are closely related to changes of blood pressure. Also, tubular sodium uptakes are controlled by any protein participating in its reabsorption and regulation, which are influenced by genetic, nutritional, metabolic and neurohormonal factors. All of these factors, alone or combination, may be able to impair the normal renal tubular sodium handling and develop high blood pressure. The investigations about the role of kidney in hypertension are shifting toward inherited as well as acquired tubular defects and further studies about renal sodium handling based on sodium transporters on the tubular segments will be needed. This review will discuss the relationship between renal sodium handling and hypertension.

Key Words : Kidney, Sodium, Hypertension

Introduction

Since the first reports of functional renal alterations in patients with essential hypertension were delivered in the 1940s[1, 2], the descriptions of more alterations in the renal handling of sodium and water were followed[3]. Body fluid maintenance and blood pressure (BP) regulation are known to be related closely. And renal sodium handling is known to be involved in those two physiologic mechanisms.

Most hypertension is the results of multiple lifestyle and metabolic and genetic interactions. Recently, many clinical and experimental studies have contributed to better understanding of role of kidney in development and maintenance of hypertension.

In 1980s, de Wardener and MacGregor suggested that essential hypertension originates from an inherited inability of the kidney to excrete a sodium load and that its development is facilitated in sodium-rich environment[4]. Nowadays, genetic studies have provided that inherited functional defects in renal sodium handling cause an increase in blood pressure.

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Renal tubular sodium handling

After circulating blood is filtrated in the glomerulus, more than 99% of the filtered sodium is reabsorbed.

In the proximal tubule, 50-60% of the total sodium transport is reabsorbed via sodium pump (Na-K ATPase) which located on the basolateral membrane (Fig. 1).

Salt sensitivity of blood pressure is defined as the interindividual difference in the blood pressure response to changes in dietary sodium chloride intake; it implies an alteration in the slope of the pressure-natriuresis curve.

Through lithium studies, the changes occurring in segmental renal sodium handling consequent to changes in the dietary sodium intake were investigated. In the group of normotensive volunteers, sodium restricted diet and sodium rich diet were

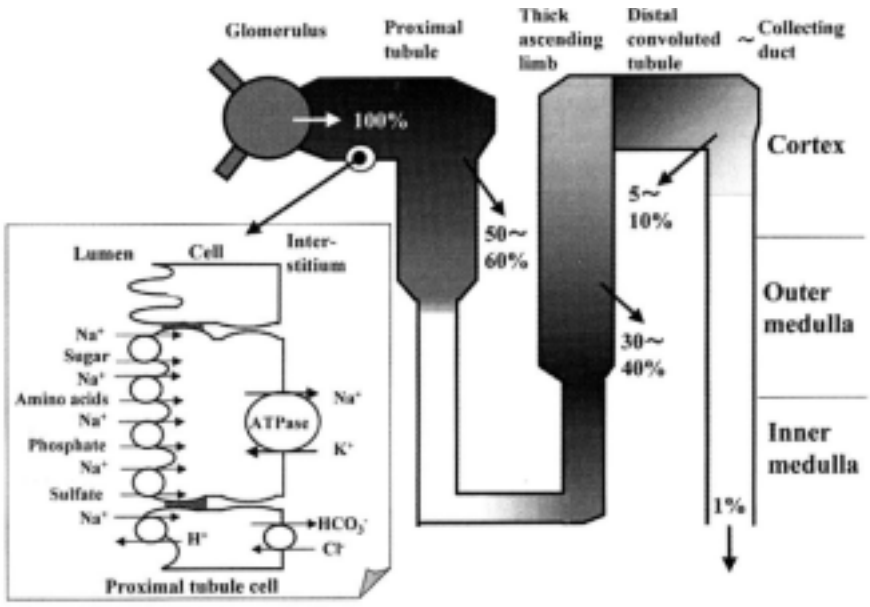

Fig. 1. *Overview of sodium transport in renal tubule and sodium transporter in porximal tubule. The intensity of sbaded areas indicatiers the activity of Na-K ATPase located in the basoleteral side of the tubular cells.*

induced. On high salt intake, fractional proximal sodium reabsorption was significantly reduced. But in the subjects whose blood pressure increased, the reduction was the least and the glomerular filtration rate was increased, suggesting a compensation mechanism to counteract the inability of the maintenance of tubular sodium balance[5].

More recently, a study performed in hypertensive patients showed that the fractional proximal sodium reabsorption reduced in salt-resistant patients and increased in salt-sensitive patients[6].

Genetic bases of the alteration in renal sodium handling in hypertension

Monogenic forms of hypertension have been described that are caused by mutations, most often associated with major alterations in the rate of renal tubular sodium chloride reabsorption[7]. These alterations seem to account for a still very small portion of high blood pressure in the population.

In most cases, the functional alterations are such as to affect sodium chloride transport in the kidney and are thus relevant to salt sensitivity of blood pressure. The Gly460Trp variant of α-adducin gene is associated with hypertension[8, 9], The patients carrying this genetic variant increase the rate of sodium reabsorption in the proximal tubule.

The other functional mutation is glucagons receptor (GCGR) gene[10], which is associated with reduced receptor affinity for glucagons in liver cells, in turn, with a lower secretory rate of its intracellular messenger cAMP. The cAMP concentration in blood is reduced and so will its influence on renal proximal sodium transport, and then is happened defective natriuresis and a modification of the pressure-natriuresis relationship.

Another mutations are GRK4-γ, single nucleotide polymorphisms of G protein-coupled receptor kinase and SGK1, serum and glucocorticoid related kinase.

The former is that the increased activity is resulted to increase in receptor phosphorylation, resulting in the uncoupling of the dopamine-1 receptor from G protein/effector enzyme complex in renal proximal tubular cellsThe later stimulates the expression of epithelial sodium channels on binding of aldosterone to own receptor, thus promoting sodium chloride reabsorption.

Metabolic and neurohormonal abnormalities associated with altered tubular sodium handling and hypertension. Some studies suggested that obesity is significantly associated with altered pressure-natriuresis relationship and may increase salt sensitivity of blood pressure[11-13]. The segmental tubular sodium handling is related to body mass and body fat pattern.

As the values of body mass index and waist circumference are increased, fractional proximal sodium reabsorption also increased.

On the other hand, abdominal adiposity than arm circumference is more related to alterations of fractional proximal sodium reabsorption.

Several mechanisms may be responsible for enhanced tubular sodium reabsorption in relation to central adiposity. Neural, endocrine, paracrine, physical activity can relate to it. One important factor is insulin which has an acute antinatriuretic effect. So acute hyperinsulinemia can develop sodium retaining effect.

In obesity, enhanced renal symphathetic tone and alterations in intrarenal physical forces may be related to enhanced tubular sodium and water reabsorption.

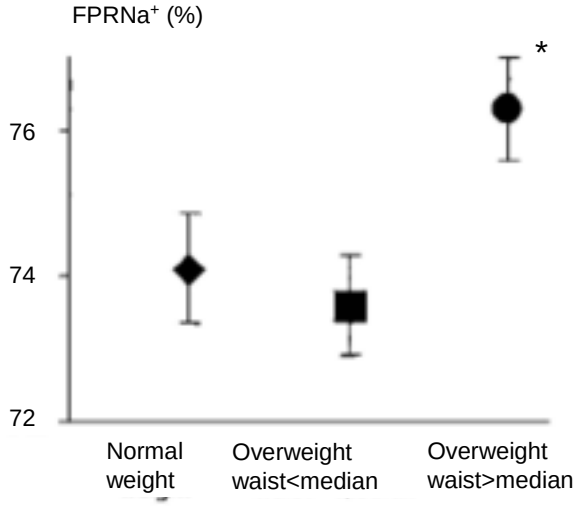

*Fig. 2. Rate of fractional proximal sodium reabsorption in normal-weight individuals (n=173) versus overweight participants with waist circumferences values either below (n=102) or above (n=167) the median for the population. Results obtained in the Olivetti Heart Study population. *p<0.01.*

Conclusion

Overall, the kidney plays an important role in the blood pressure regulation primarily by modulating tubular sodium reabsorption. In this process, various hormone, vasoactive peptide, transporter channels in renal tubule are involved.

Also, though it is accounted in small portion of essential hypertension, gene mutations associated with renal tubular sodium handling are related to the development of hypertension.

Although the detailed mechanisms have yet to be elucidated, the recognition that gene variation which results in increased sodium reabsorption in renal tubule produces hypertension may be the fundamental step for understandings to understand the pathogenic mechanisms of hypertension.

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