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Renal Redox Balance and Na^+, K^+-ATPase Regulation: Role in Physiology and Pathophysiology

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1. Introduction

An imbalance between oxidant production and antioxidant defences has been associated with the development of several conditions such as hypertension, obesity-associated hypertension and diabetes, as well as during the ageing process (Bedard & Krause, 2007; Makino et al., 2003; Touyz & Schiffrin, 2004; Valko et al., 2007; Wilcox, 2005). This association is achieved through direct reactive oxygen species damage upon biomolecules or reactive oxygen species-induced alterations in gene and protein regulation (Finkel, 2003; Gill & Wilcox, 2006; McCubrey et al., 2006; Valko et al., 2007).

Being the kidney an organ severely affected in the above-mentioned conditions, most likely tissue redox balance has implications in renal physiology and pathophysiology. In this Na^+,K^+-ATPase is especially important since it is a key molecule in renal electrolyte regulation. As such, this chapter concerns the regulation of Na^+,K^+-ATPase by reactive products of oxygen metabolism and its physiological and pathophysiological implications. Focus is given to NADPH-oxidase derived reactive oxygen species, since they appear to be important for the redox-signal, and to superoxide dismutases, for being the anti-oxidant molecules that most efficiently scavenge and remove reactive oxygen species.

This chapter begins with a brief introduction to the basic principles of renal function, Na^+,K^+-ATPase structure and mechanisms of regulation, followed by a short review on renal reactive oxygen species production and anti-oxidant defence. An exploration of the new findings and ideas on the dynamic interplay between renal redox balance, the molecular effects at the cellular level and Na^+,K^+-ATPase function is approached more deeply in the following section. Finally, experimental animal models supporting that loss of redox balance and altered Na^+,K^+-ATPase function contribute to the development of renal associated pathologies is addressed. The chapter ends with a broad overview, given in the conclusion section.

2. The kidney function and Na^+, K^+-ATPase

In an adult organism the kidney plays an important role in the regulation of blood pressure, nutrient and electrolyte reabsorption and drug and metabolite excretion. This is achieved due

to the presence of specialized proteins that are distributed into specific domains of the apical or basolateral membrane of the distinct nephron segments (Abdolzade-Bavil et al., 2004).

Na^+,K^+-ATPase is the major transporter of sodium ions in renal basolateral epithelia throughout the nephron and one of the most important renal transporters (Jaitovich & Bertorello, 2010). Na^+,K^+-ATPase is an oligomeric transmembrane protein composed of two main subunits, α and β (Figure 1). The α-subunit is the catalytic domain of Na^+,K^+-ATPase and contains the binding site for sodium ions, potassium ions, ATP, steroid hormones and phosphorylation sites for protein kinase A and protein kinase C (Aperia, 2001; Bertorello et al., 1991; Ewart & Klip, 1995; Feraille & Doucet, 2001; Schwartz et al., 1988). The β-subunit is involved in enzyme maturation, localization to the plasma membrane and stabilization of the potassium-occluded intermediate (Geering, 2008). A third subunit has been recently described to bind α and β complex in some tissues, such as heart, kidney and brain. This subunits belongs to the FXYD proteins, a group of structurally similar polypeptides expressed in a tissue-specific manner, and modulates cation binding affinity to Na^+,K^+-ATPase (Crambert & Geering, 2003; Geering, 2006; Geering et al., 2003).

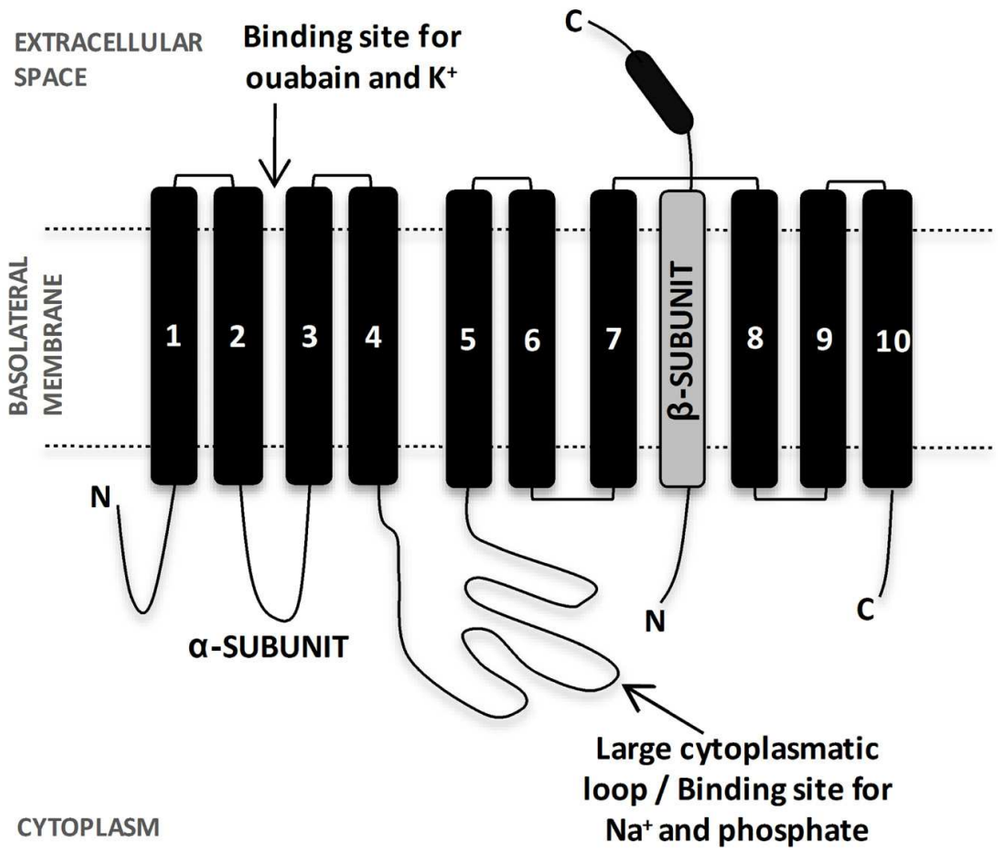

Fig. 1. Schematic representation of Na^+,K^+-ATPase. Na^+,K^+-ATPase is composed of two main subunits: a catalytic α-subunit (black) and a glycosylated β-subunit (grey).

There are 4 known isoforms of the α-subunit: α_1, α_2, α_3 and α_4, all with a unique tissue distribution. The α_1-isoform is expressed ubiquitously (Blanco & Mercer, 1998), and it is the major isoform expressed in the kidney (Kaplan, 2002).

The β-subunit has 3 known isoforms: β_1, β_2 and β_3. Detection of the tissue distribution of the β-subunit isoforms has been more difficult due to the lack of specific antibodies. However, antibody sensitivity has been improved by deglycosylation of the β-subunit. Current knowledge is that the β_1-isoform is expressed in most tissues, including the kidney (Vagin et al., 2007). The tissue specific distribution of α and β subunits indicates that each combination exhibits unique cellular functions.

In the kidney, Na^+,K^+-ATPase catalyzes ATP-dependent transport of three sodium ions in exchange for two potassium ions, maintains intracellular ion balance and membrane potential and is also responsible for maintaining sodium gradient. Thus providing the driving force for nutrients, electrolytes and water reabsorption (Aperia, 2001; Feraille et al., 2001; Kaplan, 2002; Skou, 1957). In the renal proximal tubules Na^+,K^+-ATPase plays an essential role in the bulk reabsorption of sodium and sodium-dependent reabsorption of nutrients and other electrolytes (Feraille et al., 2001) (Figure 2). Despite approximately 70% of sodium and potassium being reabsorbed in the proximal tubules the final adjustment is made in the distal tubules and the collecting ducts, where Na^+,K^+-ATPase also plays a crucial role.

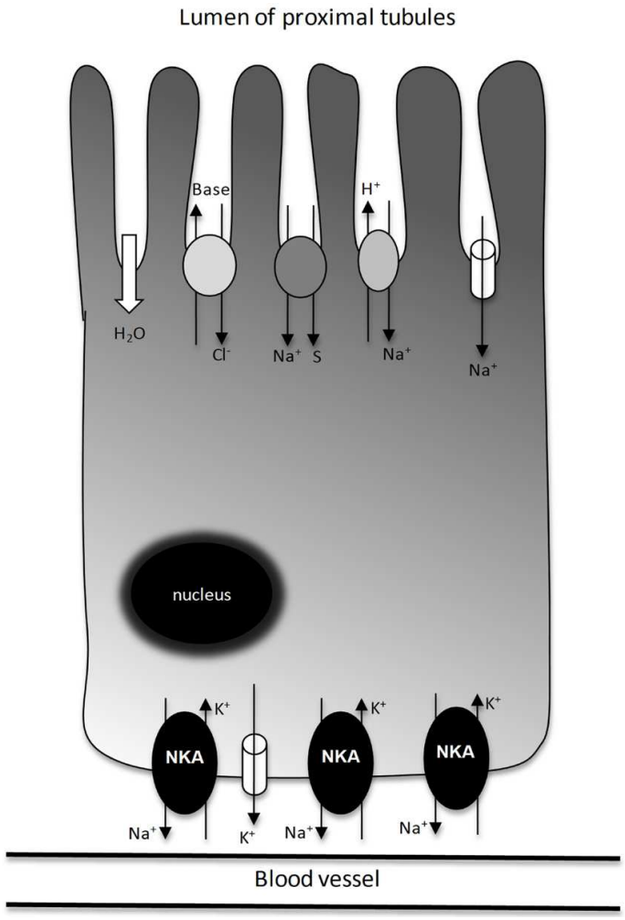

Fig. 2. Schematic representation of solute transport in the proximal tubules. A sodium gradient produced by the Na^+,K^+-ATPase allows sodium and organic substrates (S –sugars; amino acids; organic anions) to be transported into the cell. K^+ is recycled across basolateral membrane through K^+ channels.

Given the key role of Na^+,K^+-ATPase for normal renal function changes in Na^+,K^+-ATPase regulation are associated with the development of several conditions such as hypertension, obesity-associated hypertension and diabetes as well as during the ageing process (Jaitovich et al., 2010; Silva et al., 2010; Vague et al., 2004; Wang et al., 2009). As such understanding the mechanisms involved in regulation of Na^+,K^+-ATPase throughout the nephron is of major importance.

Renal Na^+,K^+-ATPase is regulated by several hormones such as dopamine, noradrenaline, aldosterone and ouabain, growth factors, peptides, several cytoskeleton proteins such as ankyrins, spectrins, adducins, actin and moesin (Aperia, 2001; Cantiello, 1997; Devarajan et al., 1994; Kraemer et al., 2003; Nelson & Veshnock, 1987; Therien & Blostein, 2000; Tripodi et al., 1996; Zhang et al., 1998) and more directly by ionic distribution across the membrane (Aperia, 2001; Feraille et al., 2001; Haber et al., 1987; Therien et al., 2000; Xie & Askari, 2002; Xie & Cai, 2003; Zhou et al., 2003). These regulatory factors may alter Na^+,K^+-ATPase function through interference with protein synthesis, insertion in membrane compartments, enzyme internalization and substrate affinity. Protein kinases, calcium, cAMP and reactive oxygen species are known secondary messengers involved in Na^+,K^+-ATPase regulation. In comparison to the other secondary messengers, little was known about reactive oxygen species-mediated Na^+,K^+-ATPase regulation and much information has been gathered in the last decade.

3. Renal reactive oxygen species generation and anti-oxidant defence

Reactive oxygen species are now looked at as normal products of cell metabolism used in various physiological functions and recognised for playing a dual role as both harmful and beneficial to the organism (Valko et al., 2007; Valko et al., 2006). Produced in low/moderate concentrations reactive oxygen species may be important mediators in cellular responses to noxia, in the defence against infectious agents, in cellular signalling pathways and in the induction of a mitogenic response (Finkel & Holbrook, 2000; Gill et al., 2006; McCubrey et al., 2006; Valko et al., 2007).

An imbalance between reactive oxygen species production and anti-oxidant defence leads to the disruption of redox homeostasis and is defined as oxidative stress. Oxidative stress is a deleterious process that can induce damage to cell structures (lipids, membranes, proteins and DNA) and lead to cellular dysfunction and eventually cell death (Harman, 1956).

Reactive oxygen species encompass a series of oxygen intermediates that include the superoxide anion, hydrogen peroxide, the hydroxyl radical and hypochlorous acid. In the organism they can be produced by xanthine oxidase, NADPH-oxidase, mitochondrial oxidative phosphorylation, lypoxygenase, cytochrome P450 mono-oxygenase and heme-oxygenase 1 (Figure 3).

Despite the existence of several sources of reactive oxygen species, NADPH-oxidase appears to be especially important for the redox-signal (Gill et al., 2006; Lassegue et al., 2001). Seven NADPH-oxidase isoforms with tissue specific distribution have been identified: NOX1, NOX2, NOX3, NOX4, NOX5, DUOX1 and DOUX2. NOX1, NOX2, NOX3 and NOX4 form heterodimers with membrane $p22^{phox}$, that stabilizes the NOX proteins and docks cytosolic specific regulatory and activator subunits needed for NADPH-oxidase function (Bedard et al., 2007; Gill et al., 2006; Nauseef, 2008). NOX1 activity requires cytosolic NOXO1, in some

cases $p47^{phox}$, NOXA1, and Rac. NOX2 activity requires cytosolic $p47^{phox}$, $p67^{phox}$, and Rac. Moreover, $p40^{phox}$ may also contribute to activation of NOX2. NOX3 activity requires NOXO1. NOX4 is active without cytosolic subunits. NOX5, DUOX1, and DUOX2 are activated by calcium and do not appear to require cytosolic subunits (Bedard et al., 2007).

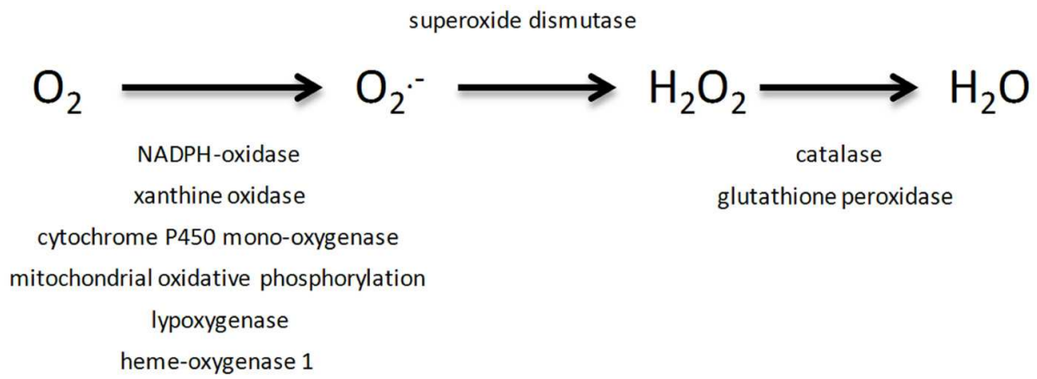

Fig. 3. Schematic representation of the balance oxidant and anti-oxidant enzymes. Multiple enzymes may induce reactive oxygen species generation that in the organism is efficiently detoxified by anti-oxidant enzymes.

Most of NADPH-oxidase isoforms are responsible for the generation of superoxide anion. However, there is still some debate on whether NOX4 generates hydrogen peroxide or superoxide anion that rapidly dismutates into hydrogen peroxide (Bedard et al., 2007; Gill et al., 2006).

The kidney is known to express at least 4 NADPH-oxidase isoforms: NOX1, NOX2, NOX4, NOX5 and NADPH-oxidase regulatory subunits (Bedard et al., 2007; Gill et al., 2006). Despite receiving considerable attention, little is known about NADPH-oxidase function in normal renal physiology (Bedard et al., 2007; Lambeth, 2007). It has been suggested that NADPH-oxidase family may play a role in secretion of erythropoietin, regulation of blood pressure by reaction of superoxide with nitric oxide limiting nitric oxide relaxing effect on afferent arterioles, alteration of cell fate through MAPK pathways activation, induction of apoptosis or cell hypertrophy through ERK 1/2 activation, regulation of gene expression by activation of transcription factors such as NF-kB or c-jun, and innate immunity (Cui & Douglas, 1997; Dorsam et al., 2000; Gorin et al., 2004; Lodha et al., 2002; Lopez et al., 2003; Rhyu et al., 2005; Wilcox, 2003). Renal NADPH-oxidase activity is influenced by diverse stimuli such as angiotensin II, chemokine receptors and aldosterone (Bedard et al., 2007; Cave et al., 2006; Dworakowski et al., 2006; Gill et al., 2006; Lambeth, 2007; Lambeth et al., 2007).

Under physiological conditions renal reactive oxygen species production is largely contained by a complex and efficient array of antioxidant defence systems. These include antioxidant free radical scavengers such as ascorbate, vitamin E, C and A and antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase. Renal superoxide dismutase can rapidly dismutate cellular superoxide anion into hydrogen peroxide that is converted to water and molecular oxygen by catalase or glutathione peroxidase (Figure 3).

Transduction of the chemical reactive oxygen species signal into biological relevant events can occur through a stable sulfenic acid modification of cysteine residues in selected proteins, resulting in protein function alterations (Cave et al., 2006; Finkel, 2003; McCubrey et al., 2006). Once oxidized, proteins can undergo spontaneous or enzymatic reduction back to the initial conformation. This mechanism represents a form of signal transduction similar to phosphorylation.

A large number of proteins have been identified as specific targets of reversible oxidation, including structural proteins, transcription factors, membrane receptors, ion channels, protein kinases and protein phosphatases (Bedard et al., 2007; Cave et al., 2006) (Figure 4). Protein tyrosine phosphatases are probably the best studied, since they control the phosphorylation status of numerous signal-transducing proteins (Finkel, 2003; Meng et al., 2002). Reactive oxygen species-induced oxidation of protein tyrosine phosphatases decreases phosphatase activity by altering the tyrosine/phosphatase balance and thereby influencing signal transduction (Figure 4). This mechanism constitutes an indirect way of reactive oxygen species-mediated activation of the mitogen activated protein kinases signal pathway. However, a direct mechanism of activation of these pathways is also possible through reactive oxygen species-induced activation of membrane receptors, such as

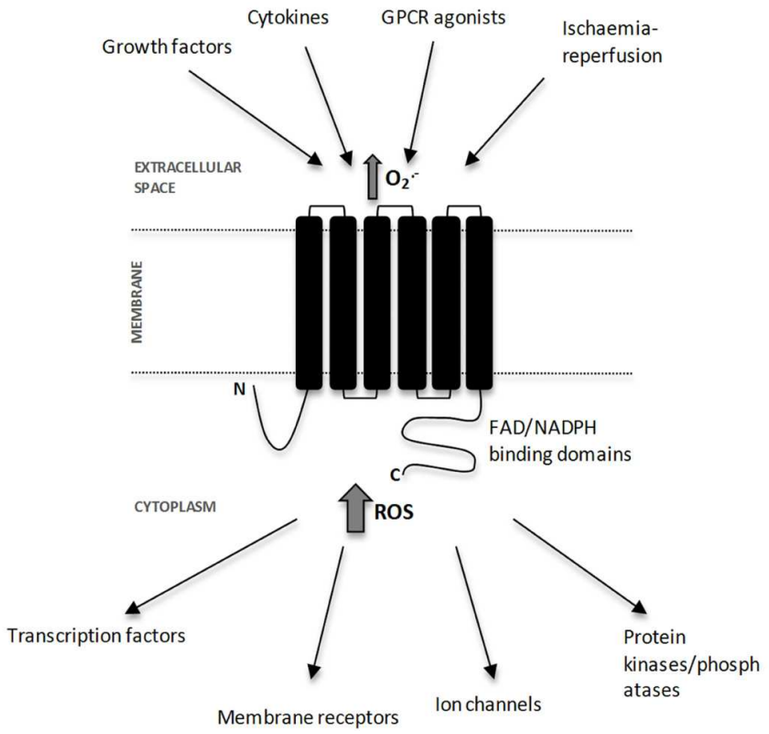

Fig. 4. Schematic representation of known activators of NADPH-oxidase isoforms and downstream effects of NADPH-oxidase derived reactive oxygen species. Diverse stimuli activate NADPH-oxidase isoforms including G-protein coupled receptor (GPCR) agonists, cytokines, growth factors and ischemia-reperfusion. NADPH-oxidase derived reactive oxygen species may influence several signalling pathways through changes in the activity of structural proteins, transcription factors, membrane receptors, ion channels and protein kinases/phosphatases.

endothelial growth factor receptor and platelet-derived growth factor receptor (McCubrey et al., 2006). As such, superoxide anion and hydrogen peroxide can be cell damaging or cell signalling molecules and play an important role in the renal physiology, as well as in the development of renal associated conditions such as diabetes and hypertension (Bedard et al., 2007; Makino et al., 2003; Touyz et al., 2004; Valko et al., 2007; Wilcox, 2005).

4. Redox balance and renal Na^+, K^+-ATPase regulation

Reactive oxygen species-mediated molecular mechanisms underlying Na^+,K^+-ATPase regulation may rely on an oxidative modification of the enzyme. In opossum kidney cells Na^+,K^+-ATPase activity is inhibited by acute incubation with 500 mM of hydrogen peroxide (unpublished results). This finding is in accordance with the works performed by Boldyrev *et al* (Boldyrev & Kurella, 1996) addressed at studying the kinetic parameters of the Na^+,K^+-ATPase after its partial inhibition by hydrogen peroxide. They used hydrogen peroxide in the mM concentration range and suggest that oxidized SH-groups of Na^+,K^+-ATPase interfered with the capacity of the enzyme to form active oligomers which are essential for higher Na^+,K^+-ATPase activity (Figure 5).

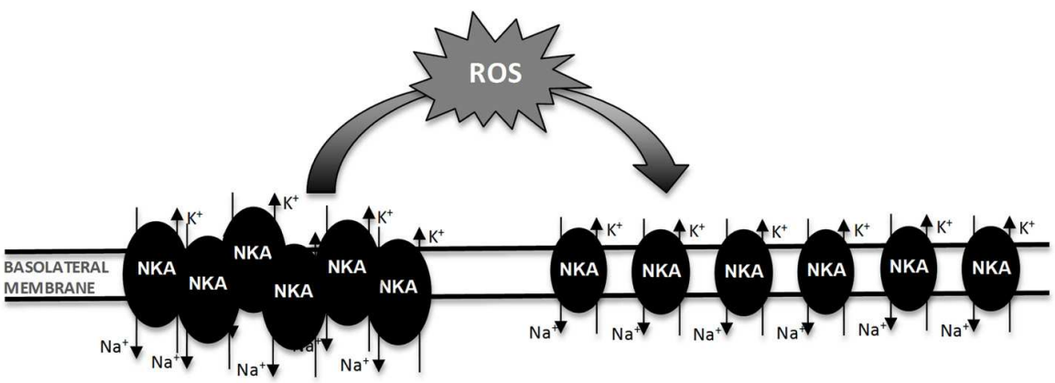

Fig. 5. Schematic representation of direct modulation of Na^+,K^+-ATPase by reactive oxygen species (ROS). ROS oxidize Na^+,K^+-ATPase interfering with the capacity of the enzyme to form active oligomers and thus decreasing Na^+,K^+-ATPase activity.

In cells reactive oxygen species are produced in specific domains, such as membrane microdomains, where NADPH-oxidase isoforms are present, or in the mitochondria. Depending on the cellular location where up-regulation of reactive oxygen species production takes place different modifications in cellular receptors and signalling pathways that alter phosphorylation, gene or protein expression can be achieved. Thus, also different outcomes regarding Na^+,K^+-ATPase activity and expression may be observed.

Reactive oxygen species-mediated alteration of cell signalling events that are participate in Na^+,K^+-ATPase regulation have been described both *in vivo* and *in vitro*. In Madin-Darby canine kidney cells it has been demonstrated that low potassium-induced an increase in Na^+,K^+-ATPase protein content and cell surface Na^+,K^+-ATPase expression (Zhou et al., 2003). The signal pathway that transduces the stimulatory effect of low potassium onto up-regulation of Na^+,K^+-ATPase is dependent on NADPH-oxidase-derived reactive oxygen

species production, Sp1 up-regulation and enhanced transcription of both α and β-subunits of Na^+,K^+-ATPase (Yin et al., 2008). Also, in opossum kidney cell line increased levels of reactive oxygen species production in cells with 80 passages in culture were responsible for up-regulation of Na^+,K^+-ATPase (Silva et al., 2006; Silva & Soares-da-Silva, 2007). Opossum kidney cells with 80 passages in culture were shown to have overexpression of NOX1, superoxide dismutase 1, superoxide dismutase 2 and superoxide dismutase 3 isoforms (Silva et al., 2007) and decreased availability to catalyze hydrogen peroxide degradation (unpublished results). When opossum kidney cells with 80 passages in culture were treated with antioxidants (apocynin or TEMPOL) Na^+,K^+-ATPase activity was found to be significantly decreased (Silva et al., 2007) (Figure 6).

In the proximal tubules of aged rats age-related increase in reactive oxygen species levels were found to be responsible for decreased basal Na^+,K^+-ATPase activity (Asghar et al., 2001; Silva et al., 2010). The molecular mechanism responsible for the observed decrease in Na^+,K^+-ATPase activity was a higher basal Na^+,K^+-ATPase phosphorylation due to reactive oxygen species-mediated increase in protein kinase C activity (Asghar et al., 2003; Asghar et al., 2001; Asghar & Lokhandwala, 2004) (Figure 6).

In the renal medulla where the final regulation of sodium and potassium in the urine takes place, ageing was accompanied by a significant increase in Na^+,K^+-ATPase activity and expression of the α_1-subunit (Silva et al., 2010). Furthermore, not only was Na^+,K^+-ATPase activity increased in renal medulla of aged Wistar Kyoto rats but also, in this part of the kidney, hydrogen peroxide production was increased with age and in comparison with renal cortex (Silva et al., 2010). Given that Na^+,K^+-ATPase regulation differs between the proximal and distal nephron segments it is possible that, in the renal medulla, increased reactive oxygen species may activate cell specific signal pathways that up-regulate Na^+,K^+-ATPase activity. In fact, a study performed by Beltowski and co-workers (Beltowski et al., 2004) investigating whether superoxide anion was involved in the regulation of renal Na^+,K^+-ATPase support this hypothesis (Figure 6). In this study, infusion of compounds modulating superoxide anion concentration into the abdominal aorta proximally to the renal rat arteries increased medullary Na^+,K^+-ATPase activity but had no effect on cortical Na^+,K^+-ATPase activity. Both apocynin and TEMPOL decreased the medullary Na^+,K^+-ATPase activity. The inhibitory effect of apocynin and TEMPOL was abolished by inhibitors of nitric oxide synthase, soluble guanylate cyclase and protein kinase G. The suggested mechanisms of Na^+,K^+-ATPase regulation is that NADPH-oxidase-derived superoxide anion increases Na^+,K^+-ATPase activity in the renal medulla by reducing the availability of nitric oxide. Other mechanism of reactive oxygen species-mediated regulation of Na^+,K^+-ATPase has been described by the same group. They reported that leptin-induced stimulation of renal Na^+,K^+-ATPase involves hydrogen peroxide generation, Src kinase, transactivation of the EGF receptor, and stimulation of ERK (Beltowski et al., 2006; Wojcicka et al., 2008) (Figure 6). However, the mechanism of Na^+,K^+-ATPase regulation in leptin-treated rats shifts from hydrogen peroxide/ERK-dependent to superoxide anion/nitric oxide-dependent after 8 days of treatment, due to a decrease in superoxide dismutase activity and as a consequence higher cellular levels of superoxide anion (Beltowski, 2010; Beltowski et al., 2008).

Finally, reactive oxygen species have also been demonstrated to alter Na^+,K^+-ATPase activity due to interference with membrane receptor function (Figure 6). Asghar et al (2004)

demonstrated that dopamine was unable to inhibit Na^+,K^+-ATPase activity in old rats and treatment with antioxidants restored the coupling of dopamine type 1 receptor to G proteins. Further studies allowed the identification of the mechanism responsible for decoupling of dopamine type 1 receptor from G proteins (Asghar & Lokhandwala, 2006; Fardoun et al., 2007). In renal proximal tubules increased reactive oxygen species production activates NF-KB and promotes its translocation to the nucleus, where it increases transcription of protein kinase C. This causes an increase in protein kinase C expression and activity, which leads to GRK-2 translocation to the membrane and subsequent dopamine type 1 receptor hyper-phosphorylation and uncoupling from protein G.

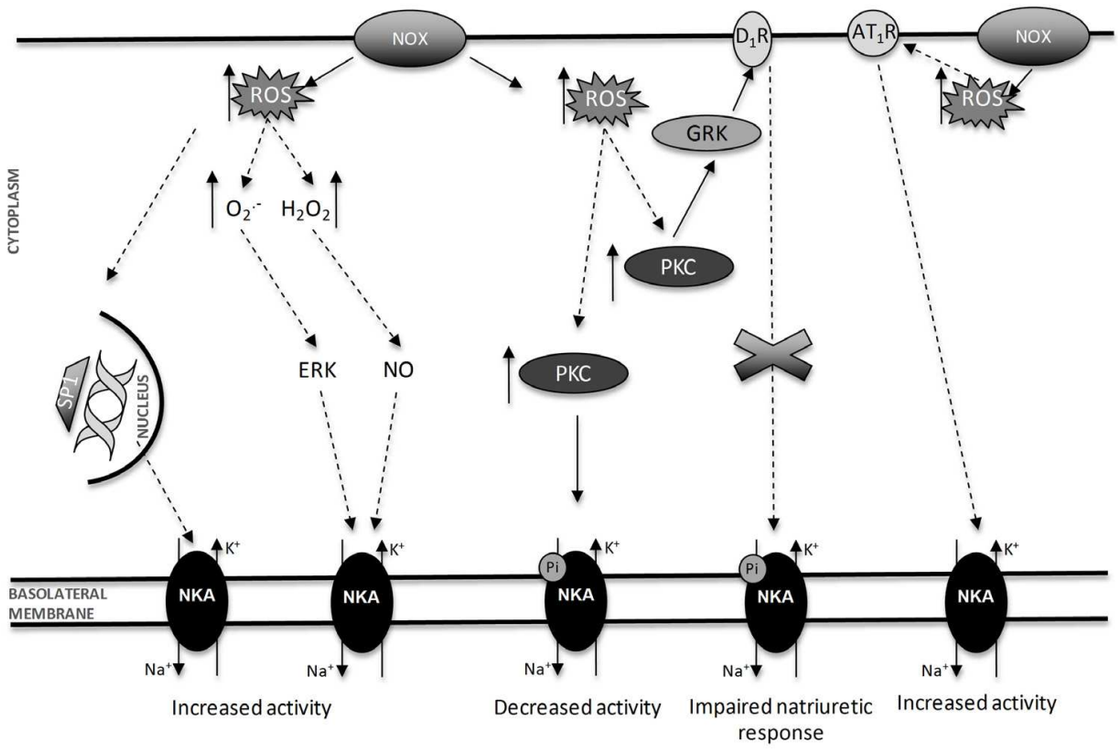

Fig. 6. Schematic representation of reactive oxygen species-mediated modulation of Na^+,K^+-ATPase. An increase in cellular levels of reactive oxygen species, mainly due to increase activity of NADPH-oxidase, activates specific cell signal cascades that interfere with Na^+,K^+-ATPase function. Filled arrows indicate a direct action. Dashed arrows indicate that the pathway is not known or was simplified.

5. Loss of redox balance: Functional consequences in renal physiology

Na^+,K^+-ATPase function in the renal proximal tubules has been a target of extensive research due to the fact that, as mentioned before, it plays a crucial role in the bulk of sodium and nutrient reabsorption. Moreover, as recently reviewed by Wang and co-workers (Wang et al., 2009) it is well known that altered renal proximal tubular sodium reabsorption is implicated in the development of essential hypertension.

In the renal proximal tubules it is well established that dopamine promotes natriuresis while angiotensin II increases sodium retention. Dopamine promotes natriureis via the activation of dopamine type 1 receptors. The dopamine type 1 receptors couple to G_s-proteins and activate the adenylate cyclase-cAMP-protein kinase A signaling pathway. In the kidney dopamine type 1 receptors can also couple to $G_{q/11}$ and activate the phospholipase C-diacylglycerol-protein kinase C pathway. Both a cross-talk between the protein kinase A and protein kinase C signaling pathways or an activation of the phospholipase C-protein kinase C pathway by protein kinase A have been described (Aperia, 2000; Brismar et al., 2000; Gomes & Soares-da-Silva, 2002; Hussain & Lokhandwala, 1998; Jose et al., 2000). Thus, activation of plasma membrane dopamine type 1 receptors stimulates a tissue specific signal cascade that leads to the activation of the protein kinase C δ-isoform. Protein kinase C δ-isoform phosphorylates the α_1-subunit of Na^+,K^+-ATPase producing a conformational change of amino-terminal, which through interaction with other domains of the α_1-subunit of Na^+,K^+-ATPase exposes the binding domains for phosphoinositide 3-kinase and adaptor protein-2. Binding of these proteins induces the activation of Na^+,K^+-ATPase endocytosis in the proximal tubules and promotes natriuresis (Cinelli et al., 2008; Efendiev et al., 2003; Pedemonte et al., 2005). Angiotensin II exerts an anti-natriuretic effect via the activation of angiotensin II type 1 receptors. Angiotensin II type 1 receptors are predominantly coupled to G-proteins and signal through phospholipases, inositol-phosphatases, calcium channels and serine/threonine and tyrosine kinases. Activation of plasma angiotensin II type 1 receptors stimulates a tissue-specific signaling cascade that leads to the activation of the protein kinase C β-isoform. The protein kinase C β-isoform phosphorylates the α_1-subunit of Na^+,K^+-ATPase producing a conformational change that increases the interaction between the α_1-subunit of Na^+,K^+-ATPase and adaptor protein-1, which results in the recruitment of the enzyme to the plasma membrane (Efendiev et al., 2000; Efendiev et al., 2003).

A reactive oxygen species-associated defect in renal dopamine type 1 receptor function has been observed not only in experimental models of hypertension (Banday et al., 2008; Hussain et al., 1999; Hussain & Lokhandwala, 1997a; Hussain & Lokhandwala, 1997b) but also in diabetes (Banday et al., 2005; Marwaha & Lokhandwala, 2006) and ageing (Fardoun et al., 2006; Hussain et al., 1999; Vieira-Coelho et al., 1999). Failure of dopamine to modulate sodium reabsorption results in diminished natriuresis and blood pressure elevation. More recently it was also demonstrated that reactive oxygen species-mediated angiotensin type 1 receptor up-regulation increases sodium transporters and subsequently contributes to sodium retention and blood pressure elevation (Banday & Lokhandwala, 2008a; Banday & Lokhandwala, 2008b). Angiotensin type 1 receptor up-regulation has been observed in experimental models of hypertension (Reja et al., 2006).

Interest in the regulation of sodium transport in renal medulla is more recent and mainly due to the existence of a possible role in the initiation and development of several forms of experimental hypertension (Cowley & Roman, 1996; Cowley et al., 1992). In renal medulla reactive oxygen species appear to directly alter sodium reabsorption and indirectly alter medullar blood flow, contributing to the development of hypertension (Cowley, 2008; Taylor et al., 2006a; Taylor et al., 2006b). One of the main sources of superoxide anion in this part of the kidney is NADPH-oxidase. NADPH-oxidase–derived superoxide anion was found to contribute to the development of salt-induced hypertension in Dahl salt-sensitive rats (Taylor et al., 2006a). A functional consequence of elevations of superoxide anion within the renal medulla was found to be an immediate reduction of sodium excretion. In this setting, Na^+,K^+-ATPase may play a role since renal medullary superoxide anion can increase

Na^+,K^+-ATPase activity by reducing availability of nitric oxide, as previously described (Beltowski et al., 2004). This mechanism may contribute to an increase in sodium reabsorption and the development of hypertension.

It is now evident that by disrupting several mechanisms responsible for maintenance of sodium homeostasis reactive oxygen species can contribute to the development of renal pathologies and hypertension.

6. Conclusion

Reactive oxygen species-mediated regulation of Na^+,K^+-ATPase has been receiving considerable attention. There is now an increasing number of publications addressing multiple mechanisms by which reactive oxygen species may alter Na^+,K^+-ATPase function and contribute to the development of several conditions, with special focus being given to hypertension. However, many intermediate events in the mechanisms of reactive oxygen species-mediated regulation of Na^+,K^+-ATPase are still unknown and much work needs to be done. Moreover, given that normalization of the redox imbalance in the proximal and distal nephron segments may require the use of specific anti-oxidant molecules and/or pharmacological modulation of different signaling pathways attention should be paid in future therapeutic approaches.

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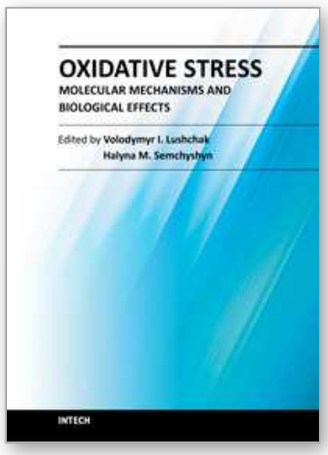

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Since the discovery of free radicals in biological systems researchers have been highly interested in their interaction with biological molecules. Denoted in 1980, and due to fruitful results and ideas, oxidative stress is now appreciated by both basic and applied scientists as an enhanced steady state level of reactive oxygen species with wide range of biological effects. This book covers a wide range of aspects and issues related to the field of oxidative stress. The association between generation and elimination of reactive species and effects of oxidative stress are also addressed, as well as summaries of recent works on the signaling role of reactive species in eukaryotic organisms. The readers will gain an overview of our current understanding of homeostasis of reactive species and cellular processes they are involved in, as well as useful resources for further reading.

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