<div align="center">**MINIREVIEW**</div>

Renal Interactions of Renin-Angiotensin System, Nitric Oxide and Superoxide Anion: Implications in the Pathophysiology of Salt-Sensitivity and Hypertension

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Summary

Renin-angiotensin system (RAS) plays a key role in the regulation of renal function, volume of extracellular fluid and blood pressure. The activation of RAS also induces oxidative stress, particularly superoxide anion (O_2^-) formation. Although the involvement of O_2^- production in the pathology of many diseases is known for long, recent studies also strongly suggest its physiological regulatory function of many organs including the kidney. However, a marked accumulation of O_2^- in the kidney alters normal regulation of renal function and thus may contribute to the development of salt-sensitivity and hypertension. In the kidney, O_2^- acts as vasoconstrictor and enhances tubular sodium reabsoption. Nitric oxide (NO), another important radical that exhibits opposite effects than O_2^-, is also involved in the regulation of kidney function. O_2^- rapidly interacts with NO and thus, when O_2^- production increases, it diminishes the bioavailability of NO leading to the impairment of organ function. As the activation of RAS, particularly the enhanced production of angiotensin II, can induce both O_2^- and NO generation, it has been suggested that physiological interactions of RAS, NO and O_2^- provide a coordinated regulation of kidney function. The imbalance of these interactions is critically linked to the pathophysiology of salt-sensitivity and hypertension.

Key words

Renin-angiotensin system • Superoxide anion • Nitric oxide • Renal function • Salt-sensitivity • Hypertension

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Introduction

In recent years, the pathophysiological aspects of excessive salt intake as an important contributor to the high prevalence of cardiovascular diseases including hypertension have been investigated in many studies (Franco and Oparil 2006, Mancia *et al.* 2007). Responsible mechanisms have been examined in clinical as well as experimental research by evaluating the responses during manipulation of dietary sodium intake (Hall *et al.* 1980, Jackson and Navar 1986, Sagnella *et al.* 1989, Midgley *et al.* 1996, Poch *et al.* 2001). The blood pressure response to changes in salt intake displays an individual variability leading to salt resistance or salt sensitivity (Weinberger *et al.* 2001, Haddy 2006). A various salt intake induces changes in regulation of sodium and extracellular volume homeostasis particularly by the kidney (Guyton *et al.* 1972). The renal hemodynamic and tubular function maintaining physiological sodium and extracellular fluid volume are regulated by several systems such as renin-angiotensin system (RAS), system of nitric oxide (NO) and reactive oxygen species (ROS), primarily superoxide anion (O_2^-) (Romero and Reckelhoff 1999).

It is generally recognized that RAS plays an important role in the regulation of blood pressure and renal function (Hall *et al.* 1980, Jackson and Navar 1986, Poch *et al.* 2001). In the kidney, the key role of RAS in the regulation of sodium and extracellular fluid homeostasis has been studied extensively and an inverse relationship between salt intake and RAS activity at

physiological state is now well established (Barri and Wilcox 1998, Husková *et al.* 2006). The relationship between fluid volume, sodium and endogenous RAS activity is critical for maintenance of normal blood pressure level. An enhanced activity of RAS can alter this relationship leading to the development of hypertension (Navar 2004, Kopkan *et al.* 2005, Husková *et al.* 2006). Angiotensin II (ANG II), as a major vasoactive agent, is responsible for physiological as well as pathophysiological effects of RAS (Navar 2004). Moreover, ANG II is a known stimulus for the formation of O_2^- via activation of NAD(P)H oxidase (Nox) enzyme (Rajagopalan *et al.* 1996, Romero and Reckelhoff 1999). Three different Nox isoforms have been isolated in the kidney: Nox1, gp91^{phox} called also as Nox2 and Nox4; however, Nox4 seems to be most abundant (Gill and Wilcox 2006). Nox enzymes are expressed along the renal vessels and nephrons and Nox activity is upregulated not only by ANG II but also by high salt intake (Hannken *et al.* 1998, Kitiyakara *et al.* 2003). Although O_2^- is produced by many other oxidizing enzymes and mitochondria, their induction by ANG II or high salt is not clearly defined. Furthermore, prolonged effects of both ANG II and high salt diet can reduce the expression of defense system against O_2^- such as superoxide dismutase (Chabrashvili *et al.* 2003, Kitiyakara *et al.* 2003, Welch *et al.* 2005). Thus increased production of ROS and their reduced degradation can lead to the oxidative stress with wide physiological and pathophysiological consequences. In the kidney, it has been clearly shown that increased O_2^- activity induces vasoconstriction and enhances tubular sodium reabsoptive function (Majid and Nishiyama 2002, Makino *et al.* 2002). These direct renal effects may be significantly involved in the pathophysiology of salt-sensitive hypertension.

Another system that plays an important role in the regulation of blood pressure and renal function is a group of enzymes producing NO (called NO synthases; NOS). There are three isoforms of NOS (neuronal, nNOS; inducible, iNOS and endothelial, eNOS). Although the kidney contains all three isoforms, they are expressed along the blood vessels and nephron segments differently (Bachmann *et al.* 1995, Wu *et al.* 1999, Tojo *et al.* 2000, Herrera *et al.* 2006). NO is a very short-lived active free radical that exerts a wide range of physiological action (Romero and Reckelhoff 1999, Wink *et al.* 2001, Wilcox 2005). NO is characterized as a major vasodilator agent regulating basal vascular tone and it

also inhibits renal tubular transport of sodium and thus plays an important role in overall excretory function of the kidney (Majid and Navar 2001, Wilcox 2005). Interestingly, eNOS that is considered to be the main source of NO production can be also induced by ANG II (Chin *et al.* 1999, Moreno *et al.* 2002). On the other hand, an excessive salt intake may also activate iNOS and nNOS in the kidney (Mattson and Higgins 1996, Tan *et al.* 2000, Schneider *et al.* 2008). Thus NO provides a protective role against several factors such as salt loading, oxidation or vasoconstrictors in the control of renal function (Zou *et al.* 1998, Chin *et al.* 1998, Lopez *et al.* 2003, Kopkan and Majid 2005, Červenka *et al.* 2008). The functional NO system is required for the maintenance of sodium and extracellular fluid homeostasis and any alterations in NO production lead to the impairment of organ function including the kidney.

Thus, in this minireview, we would like to focus on the current understanding of the involvement of renal interactions between RAS, NO and O_2^- in the coordinated regulation of kidney function. As a central role of the kidney in the sodium and extracellular fluid homeostasis and thus long-term blood pressure regulation is still supported by current evidence, a further aim of our minireview is to consider the consequences of imbalance in these interactions that are critically linked to the pathophysiology of salt-sensitivity and hypertension.

ANG II, NO and O_2^- interactions and renal function

Several mechanisms of the interaction between ANG II, NO and O_2^- that are involved in the regulation of kidney function have been demonstrated in many studies (Wilcox 2005, Patzak and Persson 2007). Although direct acute effect of ANG II on renal hemodynamic and excretory function is well known, new findings have been described when NO or O_2^- is pharmacologically interfered acutely. In rats (Lopez *et al.* 2003), it has been shown that acute ANG II infusion into the kidney caused a dose-dependent reduction in glomerular filtration rate (GFR) and NO level in the renal cortex. Moreover, the dose of ANG II administered into the dog kidney, that unaffected GRF under intact conditions, reduced GFR after NOS inhibition (Majid *et al.* 2005). This response was greatly attenuated by concomitant administration of a O_2^- scavenger, tempol, or Nox inhibitor, apocynin (Lopez *et al.* 2003, Majid *et al.* 2005). These data clearly indicate an interactive role of ANG II, NO and O_2^- in the

regulation of GFR, where NO displays protective properties against vasoconstrictors to maintain GFR. Furthermore, the sodium retaining effect of acute ANG II infusion was also influenced by concomitant O_2^- generation (Lopez *et al.* 2003) and such effects were greatly accelerated under the conditions of NO blockade in dogs (Majid *et al.* 2005). Acute systemic infusion of ANG II in mice lacking catalytic subunit of Nox, gp91^{phox} (gp91^{phox} KO), which exhibit lower production of O_2^-, caused a lesser degree of decreases in renal blood flow (RBF) and increases in renal vascular resistance (RVR) compared to wild-type mice (Haque and Majid 2004). These observations demonstrate that the acute renal effects of ANG II are enhanced by an increased Nox-derived O_2^- production, particularly under the conditions of NO deficiency, and they can be partially attenuated by the use of O_2^- scavengers or Nox inhibitor and also in gp91^{phox} KO mice.

　　　These *in vivo* observations are well supported by *in vitro* studies testing the resistance and responsiveness of afferent and efferent arterioles, tubuloglomerular feedback (TGF) mechanisms and tubular transport in the isolated tubules. Glomerular arterioles account for the major part of renal vascular resistance and thus play important role in the control of RBF and GFR. It has been clearly demonstrated that constrictor responses of glomerular arterioles to ANG II were increased after NOS blockade (Ikenaga *et al.* 1996a). These responses to ANG II are also attenuated by addition of superoxide dismutase or tempol to this preparation (Schoonmaker *et al.* 2000, Ozawa *et al.* 2004). Thus O_2^- appears to be partially responsible for ANG II-induced constriction of that vascular segment. Moreover, NO is diminished by increasing O_2^- and thus vasoconstriction can be further enhanced (Wilcox and Welch 2000). These interactions directly modulate the TGF mechanism and tubular function in nephrons. Although ANG II is essential for TGR responsiveness (Ikenaga *et al.* 1996b, Schnermann *et al.* 1997), its increased production leads to the exaggerated TGF responses in hypertensive animals (Huang *et al.* 1988, Brannstrom et al. 1999, Welch et al. 2000). Furthermore, O_2^- enhances the basal TGF response and limits NO signaling from the macula densa. On the other hand, NO particularly derived from the macula densa inhibits TGF to antagonize enhanced ANG II and O_2^- effects (Braam and Koomans 1995, Ichihara and Navar 1999, Wilcox and Welch 2000, Wang *et al.* 2002). The role of ANG II and NO interaction in the regulation of tubular sodium transport within nephron segments has

been studied conclusively (Wang and Giebisch 1996, Dickhout *et al.* 2002, Mori and Cowley 2003, Zhang and Edwards 2007, Silva and Garvin 2008) as these substances counteract each other. Significant finding has been made by Garvin´s group when a direct stimulatory effect of O_2^- on sodium transport in thick ascending limb of loop of Henle has been found. And this stimulatory O_2^- effect on tubules is also counteracted by NO (Ortiz and Garvin 2002a, 2002b, Juncos *et al.* 2006). Thus it is obvious that these mechanisms play an important role in the regulation of sodium excretion and may contribute in the development of salt-sensitivity and hypertension. This notion is further supported by observations that high salt intake induces production of NO as well as O_2^- in the glomerular arteries, macula densa and tubules where they modulate physiological function of the kidney (Ortiz *et al.* 2003, Varela *et al.* 2004, Abe *et al.* 2006).

　　　Collectively, these *in vivo* and *in vitro* studies propose new insights into the involvement of ANG II, NO and O_2^- interactions in the regulation of renal hemodynamics and tubular function and suggest possible mechanisms that may contribute to the development of salt-sensitivity and hypertension (Fig. 1).
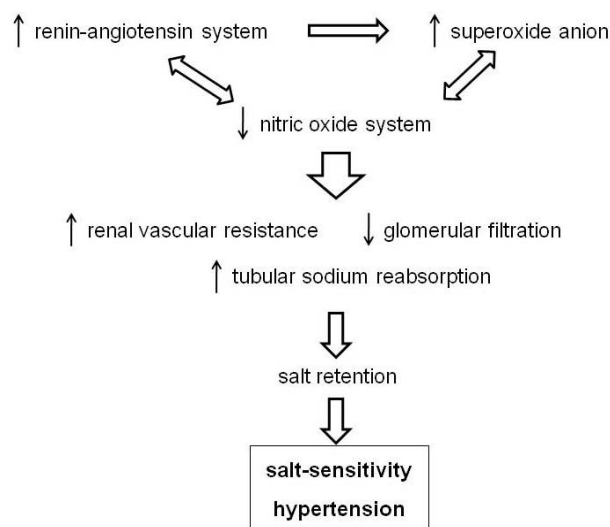

Fig. 1. Pathophysiological impact of the imbalance between renin-angiotensin system, superoxide anion and nitric oxide in the kidney.

Pathophysiological impact of RAS, NO and O_2^- interactions in ANG II-dependent hypertension

　　　Many studies have confirmed the prominent importance of RAS in the pathophysiology of

hypertension (Reckelhoff and Romero 2003, Navar 2004). Hypertension induced by chronic infusion of subpressor ANG II dose is a simple model which does not have elevated circulating or tissue renin activity. Although the enhanced plasma and mainly kidney ANG II levels has been confirmed in this model, renal hemodynamic and tubular function are maintained at relatively normal range or can be just slightly reduced (Von Thun *et al*. 1994, Wang *et al*. 1997, Kopkan *et al*. 2006). This observation strongly suggests that counteracting renoprotective mechanisms are activated. As seen in ANG II-induced hypertensive rats, NO partially counteracts the vasoconstrictor influence of elevated ANG II levels to maintain renal hemodynamics (Chin *et al*. 1998, Nishiyama *et al*. 2001). In addition, the exogenous L-arginine can significantly blunt angiotensin II-dependent hypertension and associated renal damage by increasing NO bioavailability in hypertensive animals (Rajapakse *et al*. 2008). The relation between high salt intake and blood pressure responses to chronic ANG II administration were also evaluated in rats (Sasser *et al*. 2002, Pech *et al*. 2006). As high salt intake exaggerated ANG II-induced increase in blood pressure, this model of hypertension exhibits an obvious salt-sensitivity. Moreover, the development of salt-sensitive hypertension has been demonstrated after transient exposure to ANG II in rats with progressive organ damage (Lombardi *et al*. 1999, Rodriguez-Iturbe *et al*. 2001).

There is a clear link between oxidative stress and the development of ANG II-induced hypertension (Wang *et al*. 2001, Reckelhoff and Romero 2003), but the exact mechanisms are not yet fully understood. It has been shown that production of O_2^- is enhanced *via* NAD(P)H oxidase. Moreover, defense antioxidative enzymes (superoxide dismutase, catalase and gluthatione peroxidase) in the kidney were reduced during ANG II exposure (Cifuentes *et al*. 2000, Chabrashvili *et al*. 2003, Welch *et al*. 2005, Pech *et al*. 2006). The development of hypertension induced by chronic low-dose infusion of ANG II was shown to be attenuated by chronic treatment with tempol in mice and rats (Kawada *et al*. 2002, Welch *et al*. 2005). An enhanced ROS production during chronic ANG II administration might not be only involved in the progression of organ damage. As it has been demonstrated that an enhanced O_2^- activity mediates acute renal responses to ANG II (Lopez *et al*. 2003, Haque and Majid 2004, Majid *et al*. 2005), the possible role of enhanced O_2^- generation in the regulation of renal function has examined in ANG II-induced hypertensive

rats (Kopkan *et al.* 2006). This study showed that acute tempol infusion into the renal artery in anesthetized rats increased RBF, GFR and $U_{Na}V$ in hypertensive rats, but not in normotensive rats, implying that enhanced generation of O_2^- modulates renal hemodynamic and excretory function leading to sodium retention in this model.

In the transgenic rat model of ANG II-dependent hypertension with constitutive mouse renin gene expression (TGR) which exhibits increased circulating as well as tissue ANG II levels and also oxidative stress since prehypertensive phase (Kopkan *et al.* 2005, Vaněčková *et al.* 2005), it has been observed that tempol administered directly into the renal artery acutely increased renal plasma flow (RPF) and GFR in these prehypertensive animals. Moreover, NOS inhibitor, nitro-L-arginine methylester (L-NAME) caused greater decreases in RBF and sodium excretion in prehypertensive TGR compared to age-matched control rats and these responses to L-NAME were abolished by co-administration of tempol (Kopkan *et al.* 2007). These data suggest that renal function is modulated by enhanced O_2^- generation induced by ANG II in prehypertensive TGR and further support the notion that NO serves a protective role maintaining normal renal function in this model. To examine the role of this enhanced O2- generation in the pathophysiology of hypertension in TGR, chronic antioxidant treatment was applied during the development of hypertension in these animals (Kopkan et al. 2009). However, despite of reduction in oxidative stress by tempol and apocynin administration in TGR, hypertension was not attenuated in this model. These data suggest that the markedly enhanced ANG II activity is almost entirely responsible for the development of hypertension with a negligible contribution of oxidative stress to the pathophysiology of hypertension in this model of ANG II-dependent hypertension (Kopkan et al. 2009).

In TGR, high-salt diet induced significant increases in blood pressure at all ages when compared with age-matched TGR fed normal-salt diet (Husková *et al.* 2006). Interestingly, salt-sensitive responses in early stages of hypertension were more pronounced in female than in male TGR. On the other hand, salt restriction led to lower progression of hypertension in both female and male TGR. This observation cannot be explained just by unresponsiveness of RAS activity to various levels of salt intake in these animals and thus other unknown mechanism needs to be considered (Husková *et al.* 2007). These studies indicate a strong salt-sensitive component

of hypertension with unanticipated sexual dimorphism. However, the exact role of the interaction between ANG II, NO and O$_2^-$ in the salt-sensitivity remains to be clarified in this model.

Another important model of ANG II-dependent hypertension is the two-kidney, one-clip (2K1C) Goldblatt model in which hypertension is induced by unilateral stenosis of the renal artery (Welch et al. 2003, Navar 2004, Červenka et al. 2008). The reduced renal perfusion pressure stimulates renin release from the clipped kidney triggering a whole RAS cascade with a slow progression of hypertension. Similarly to the previous models of ANG II-dependent hypertension, the augmented RAS activity leads to the induction of oxidative stress that may be involved in the pathophysiology of hypertension in this model (Lerman et al. 2001). This was further supported by acute administration of tempol that reduced RVR and increased RPF, GFR and sodium excretion in both clipped and nonclipped kidney (Guron et al. 2006). Moreover, chronic treatment with tempol reduced blood pressure and also improved renal function in the clipped kidney (Welch at el. 2003). A protective role of NO in the kidney has been also suggested in this model where enhanced NO release buffers ANG II-induced contraction of isolated afferent arteriole from the nonclipped kidney of 2K1C hypertensive rats (Helle et al. 2009). It seems that NO protective mechanism might be impaired in 2K1C hypertensive rats (Sánchez-Mendoza et al. 1998, Červenka et al. 2008). The administration of L-arginine, as a substrate for NO generation, has been shown to attenuate hypertension in 2K1C rats suggesting that NO production is insufficient in this model (Abreu et al. 1999). Moreover, treatment with losartan prevented increased vascular responses to ANG II, and this effect was associated with a restoration of NOS activity and NO release (Martinez et al. 2002). These data suggest that ANG II reduces NOS activity directly or via enhanced ROS production blunting vascular and renal effects of NO during the development of renovascular hypertension. Given together, these investigations collectively help in understanding these interactions and their possible involvement in the pathophysiology of hypertension.

Pathophysiological impact of RAS, NO and O$_2^-$ interactions in salt-induced models of hypertension

Dahl salt-sensitive rats exhibit progressive increases in arterial pressure in response to high salt intake leading to the endothelial dysfunction, inflammation and renal damage. An impaired NO system and oxidative stress have been suggested to significantly contribute to the development of hypertension in this model (Tan et al. 2000, Zicha et al. 2001, Mori et al. 2007, Zhou et al. 2009). However, exaggerated local RAS activity is also involved in the pathophysiological processes. Although Dahl salt-sensitive rats have low renin level and high salt intake suppresses plasma ANG II, it has been observed that kidney ANG II level is not decreased by high salt (Kobori et al. 2003). Moreover, high salt intake increases renal angiotensinogen level in Dahl salt-sensitive rats. This paradoxical enhancement may be an important contributor to the salt-sensitivity in this model (Kobori et al. 2003). It has been also indicated that sympathetic hyperactivity in Dahl salt-sensitive rats plays a major role in the maintenance of salt-sensitive hypertension (Zicha et al. 2001). These sympathetic responses to high salt intake are also closely associated with enhanced RAS and O$_2^-$ activity and NO deficiency and these interactions may influence renal function in hypertensive animals. There is a good agreement between these results and studies indicating that RAS inhibition attenuates hypertension, endothelial dysfunction and renal damage in Dahl rats (Tian et al. 2006, Liang and Leenen 2008, Zhou et al. 2009). Similar protective effects have been shown during antioxidant treatments, when renal function was improved in these hypertensive rats (Tomohiro et al. 1997, Tian et al. 2008).

In other salt-induced model of hypertension – deoxycorticosterone acetate (DOCA) rats – oxidative stress, insufficient NO production and local ANG II seem to play a role in the development of hypertension and impaired organ function (K-Laflamme et al. 1998, Shelat et al. 1999, Rhaleb et al. 2001, Beswick et al. 2001a, Sullivan et al. 2002, Obst et al. 2004, Erdely et al. 2007). Similarly to Dahl rats, antioxidant treatment or RAS inhibition attenuated hypertension and organ damage in DOCA-salt rats and improves endothelial dysfunction by increased NO generation in these hypertensive animals (Gross et al. 1999, Beswick et al. 2001a, 2001b, Xu et al. 2002, Ghosh et al. 2004). It could be argued that blood pressure lowering effect of O$_2^-$ scavengers such as tempol might be due to inhibition of increased sympathetic activity in DOCA rats. However, it was also demonstrated that SOD inhibition enhancing O$_2^-$ level caused stimulation of renal sympathetic activity and tempol ameliorated this effect (Shokoji et al. 2004), indicating that tempol-induced inhibition of sympathetic

activity could be related to its ability to scavenge O_2^-. In DOCA rats, it has been observed that NO plays a protective role against hypertensive DOCA effect, as orally administered L-NAME induced a further increase in blood pressure (Alvarez *et al.* 2000). These results suggest that NOS inhibition may also affect sodium retention induced by DOCA and, therefore, increases blood pressure in this model. Overall, this provides further evidence that ANG II, NO and O_2^- interactions and their impact on regulation of renal function contribute to the development of salt-sensitive hypertension.

Pathophysiological impact of RAS, NO and O_2^- interactions in NO-deficient form of hypertension

The most conclusive evidence for the essential role of NO in the regulation of blood pressure and organ function was obtained from a model using pharmacological inhibition of NO production that primarily targets the constitutive eNOS as a major source of NO under normal condition. Although this is a simple experimental model, it reveals in fact very complex mechanisms that contribute to the pathophysiology of NO-deficient hypertension (Zatz and Baylis 1998). Acute cardiovascular and renal effects of NOS inhibition have been studied intensively in many *in vivo* and *in vitro* preparations, as mentioned above. In conscious animals, chronic administration of nonselective NOS inhibitors produced sustained hypertension, increased vascular resistance and an impairment of organ function including the kidney (Baylis *et al.* 1992, Lahera *et al.* 1992, Tolins and Shultz 1994, Kopkan and Majid 2006). An activation of RAS and sympathetic tone may also account, at least in part, for the vasoconstrictor activity after NOS inhibition (Fortepiani *et al.* 1999, Pecháňová *et al.* 2004, Zicha *et al.* 2006). Moreover, an enhanced O_2^- activity has been indicated as an important contributor for the pathophysiology of NO-deficient form of hypertension (Usui *et al.* 1999, Rauchová *et al.* 2005). Although an exact explanation for the exaggerated activities of vasoconstrictor systems during NO inhibition is still indefinite, this model could afford more pathophysiological mechanisms of the imbalance between those vasoactive substances than other hypertensive models.

Previous observations have shown that NO not only counteracts the vascular effects of vasoconstrictors, but it exhibits crucial properties in the maintenance of sodium and extracellular fluid homeostasis. This notion has been further supported by observation that NO-deficient hypertensive animals evidently exhibit salt-sensitivity (Tolins and Shultz 1994, Kopkan and Majid 2005) leading to the progression of renal injury in this model (Yamada *et al.* 1996, Graciano *et al.* 2004). Interestingly, after 3 week exposure to L-NAME and the 1 week washout period, a salt-sensitive state has been still observed in rats (Quiroz *et al.* 2001). This founding was explained by irreversible renal damage and inflammation after prolong NO blockade. Furthermore, it was observed in NO-deficient animals, that this exaggerated hypertensive response to high salt intake was abolished by concomitant administration of tempol with L-NAME (Kopkan and Majid 2005). These data indicate that O_2^- contributes to the development of salt-sensitivity, which is involved in the pathophysiology of NO-deficient hypertension. The pathophysiological role of enhanced O_2^- activity in the kidney in salt-sensitive responses was more than evident in this model. Indeed, acute treatment with an O_2^- scavenger, tempol, increased RBF, GFR, and urinary sodium excretion in L-NAME-induced hypertensive rats (Kopkan and Majid 2006). Taken together, these results demonstrate that enhanced O_2^- activity under the conditions of NO deficiency modulates renal hemodynamics and excretory function, which contribute to the development of salt-sensitivity and hypertension induced by chronic NOS inhibition.

Although specific contributions of particular NOS isoforms in the regulation of renal function and blood pressure have been studied in many models of hypertension, acute and chronic administration of the potentially selective inhibitors for nNOS or iNOS have yielded inconclusive results that were mostly limited by missing selective eNOS inhibition (Ollerstam *et al.* 1997, Mattson *et al.* 1998). However, studies in genetically modified mice strongly support the notion that eNOS isoform is a predominant and essential source of NO maintaining several physiological processes in the body (Ortiz and Garvin 2003). It has been observed that knockout mice lacking the gene for the eNOS exhibit higher blood pressure and impaired vasodilator responses (Huang *et al.* 1995, Faraci *et al.* 1998), whereas deletion of the genes encoding the nNOS or iNOS isoforms did not significantly alter cardiovascular system (Ortiz and Garvin 2003). In the mouse kidney, NO derived from eNOS regulates renal hemodynamics (Mattson and Meister 2005, Patzak *et al.* 2008), but it remains to be

determined if an increased salt and fluid absorption by the kidney may be involved in the hypertension exhibited by eNOS-deficient mice. Although nNOS and iNOS may partially compensate deficient production of NO in these mice (Mattson and Meister 2006, Patzak *et al.* 2008), the study by Ortiz *et al.* (2003) suggested that eNOS mediates NO production and thus regulates sodium chloride transport in thick ascending limb. This transport mechanism is impaired in eNOS deficient mice, in which it can be reversed by eNOS gene transfer to the thick ascending limb (Ortiz *et al.* 2003). These data indicate that genetic deletion of eNOS is not compensated for the thick ascending limb by other NOS isoforms. Thus an increased blood pressure response to a high-salt diet that has been observed in eNOS-deficient mice (Leonard *et al.* 2006) is likely promoted by reduced production of NO in the tubules. It remains to be resolved whether other mechanisms such as increased O_2^- may contribute in the salt-sensitivity and hypertension in this mouse model.

Conclusions and Perspectives

This minireview demonstrates the important interactive role between RAS, O_2^- and NO in the regulation of renal hemodynamics and tubular sodium excretion and its impact on blood pressure supporting the hypothesis that imbalance between these substances may contribute to the development of salt-sensitivity and hypertension (Fig. 1). These observations suggest that the activation of RAS, which is associated with an enhanced O_2^- activity, causes reduction of NO availability leading to the disparity between oxidative and antioxidative mechanisms in the tissues, which is involved in many pathophysiological processes in the body. It should be emphasized that further experiments are needed to characterize and delineate these interactions at the enzymatic level of the production of vasoactive substances such as ANG II, oxidative and nitrosative radicals in normal conditions as well as during the development of salt-sensitive hypertension. These new findings would increase our understanding of physiological as well as pathophysiological processes of many cardiovascular and renal diseases.

Conflict of Interest
There is no conflict of interest.

Acknowledgements

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