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# Regulation of Renal Hemodynamics by Purinergic Receptors in Angiotensin II – Induced Hypertension

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## 1. Introduction

### 1.1 Effect of purinergic receptors activation on the regulation of renal hemodynamics

Extracellular ATP participates in several physiological processes such as neurotransmission, modulation of vascular tone, contraction of smooth muscle cells, aggregation of platelets and signal transmission (Burnstock, 2006). ATP, and its metabolite adenosine are characterized by their vasoactive properties in several arterial beds, including the renal microcirculation. Purinergic receptors (P1 and P2) are expressed in the cortex and medulla of kidney; P1 are mainly activated by adenosine (ADO) and P2 receptors are activated by ATP. Both, P1 and P2 receptors participate in the regulation of vascular tone and hemodynamics in the kidney microvasculature, and have an important role in the tubuloglomerular feedback mechanism. (Schnermann & Levine, 2003; Navar, 1998; Mitchell & Navar, 1993; Inscho, 2001).

Purinergic receptors P1 include four receptors subtypes, A1, A2a, A2b, and A3 (Inscho et al., 1992); A1 and A3 receptors are coupled to Gi proteins, inhibiting adenyl cyclase when these receptors are activated by its agonists, with the consequent decrease of intracellular cAMP. High affinity A1 receptors are constitutively activated in the renal vessels and induce vasoconstriction whereas the location and functional role of the A3 receptors in the kidney remains unclear. In contrast, the A2a and A2b receptors are coupled to Gs protein and interaction with exogenous adenosine produces systemic vasodilation in most of vascular beds, but paradoxical vasoconstriction in the kidney microcirculation.

In addition, adenosine has been implicated in the regulation of glomerular filtration rate and activation of the tubuloglomerular feedback mechanism (Franco, et al., 1989; Schnermann & Levine, 2003). In this regard, exogenous adenosine induces an increase in afferent and efferent resistances, which results in a fall of glomerular blood flow, glomerular capillary pressure, and ultrafiltration coefficient, leading to a decrease in single nephron glomerular filtration rate (Franco et al., 1996; Osswald, 1984). Concerning the tubuloglomerular feedback (TGF) mechanism, administration of A1 receptors blockers prevented the

glomerular capillary pressure decrease (or single nephron glomerular filtration rate) induced by the perfusion to the macula densa; these results indicate an inhibition of the TGF mechanism. In contrast, adenosine and its analogues markedly increased the glomerular capillary pressure after perfusion of the macula densa, thus enhancing the response of the TGF mechanism, an effect that seems to be related to the activation of adenosine A1 receptors. In this regard, adenosine is required for elicit a normal TGF response (Schnermann & Levine, 2003).

ATP Purinergic receptors include two types of membrane proteins, P2X and P2Y. These receptors have important structural differences; seven subtypes have been described, P2X 1-7, and these receptors are non-selective cation channels composed by two transmembrane domains that facilitate the entry of extracellular calcium. P2Y receptors include eight subtypes, P2Y 1, 2, 4, 6, 11, 12, 13, and 14; these receptors are G protein-coupled proteins with transmembrane domains associated to phospholipase C that induces the elevation of cytosolic calcium from the intracellular stores (Burnstock, 2007; Guang et al., 2007). The effect of P2 receptors depends of the cell type; P2X receptors are mainly located in the smooth muscle cells and P2Y receptor are predominate in the endothelial cells. P2X receptor activation in the smooth muscle cells produces renal vasoconstriction; in the endothelial cells only P2X4 has been described as able to induce vasodilation. P2Y receptor activation in the endothelial cells induces vasodilation, and by release of nitric oxide or prostaglandin I<sub>2</sub> (Wihlborg et al., 2003), whereas in the smooth muscle cells induces vasoconstriction through increasing intracellular calcium release.

The ATP vascular effects are difficult to evaluate due to the degradation of this molecule to adenosine by ectonucleotidases, as well as to the enhanced endothelial production of nitric oxide induced by ATP. The nucleotide induces renal vasoconstriction in rabbits and rats; infusion of ATP produces an inconsistent decrease in the glomerular capillary pressure that becomes a sustained vasoconstriction under blockade of adenosine receptors (Mitchell & Navar, 1993). However in dogs, infusion of ATP into the renal artery produces an increase in renal blood flow; in this model, when nitric oxide production is blockaded before the ATP infusion, the renal vasodilation is impaired. These changes are due to the differential effect of P2Y receptors stimulation on endothelial and smooth muscle cells; P2Y receptors enhance the production of nitric oxide by endothelial cells, but the direct activation of P2X receptors in the vascular smooth muscle cells induce vasoconstriction in the renal microcirculation (Inscho, 2009). On the other hand, ATP inhibits the tubuloglomerular feedback response; the mechanism of such inhibition is still unclear but it has been demonstrated that it is not mediated by degradation of the nucleotide to adenosine (Mitchell & Navar, 1993). In other words, it likely that extracellular ATP contributes to the regulation of TGF responsiveness.

In the isolated juxtamedullary nephron preparation, ATP induces an initial vasoconstriction of the afferent arterioles (Inscho et al., 1995; Inscho et al., 1996) that wanes and finally remains a residual vasoconstriction, as observed in "in vivo" studies; the blockade of adenosine receptors increases the ATP-mediated vasoconstriction. The ATP vasoconstrictor effect was maintained during the blockade of nitric oxide, supporting the notion that stimulation of P2Y receptors induce an initial vasoconstriction that is counterbalanced by a later NO release, resulting in a transient vasoconstriction induced by ATP (Inscho et al., 1994). In contrast to the effects on afferent arterioles, the efferent arteriole does not respond to ATP, which suggests a low number of P2 receptors (Inscho et al., 1994; Chan et al, 1998).

## 2. Renal hemodynamics in the Ang II-infused hypertensive rat

Angiotensin II-induced hypertension is characterized by elevated intrarenal Ang II levels, renal vasoconstriction and renal injury (Zou et al., 1996; Shao et al., 2009; Franco et al., 2001, Johnson et al., 1992, Arendshorst et al., 1999). As previously observed in this model, systolic blood pressure increased through the 14 days infusion period and was associated with a marked proteinuria (Figure 1), as well as a dramatic fall in urinary nitrate excretion.

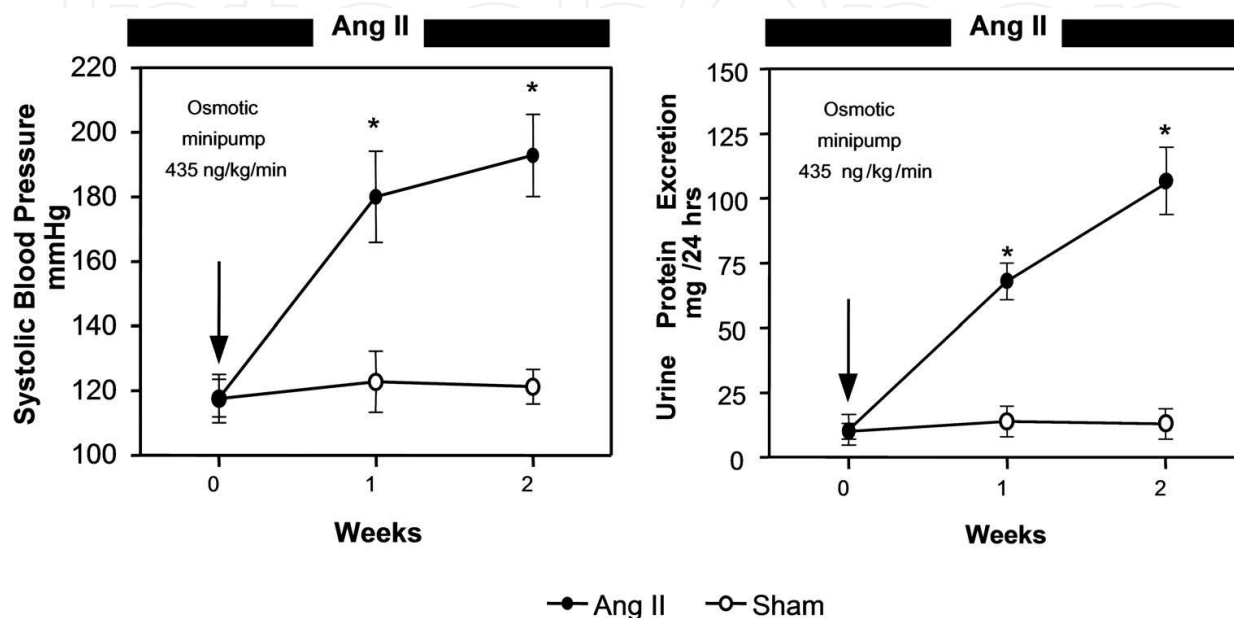


Fig. 1. Follow up of systolic blood pressure and proteinuria during 14 days after Ang II was infused by an osmotic minipump (modified from Franco et al. 2001).

This hemodynamic pattern in the Ang II-induced hypertension is similar to the changes produced by acute infusion of the peptide (Blantz et al., 1976). After 14 days of Ang II infusion, glomerular hemodynamics is characterized by intense renal vasoconstriction, with a decrease in total glomerular filtration rate. At the single nephron level, a marked elevation of afferent resistance and a mild increase of efferent resistance are observed; the increase in resistances lead to a fall in glomerular plasma flow and ultrafiltration coefficient (K<sub>f</sub>); as a result, the single nephron glomerular filtration rate was markedly reduced as a consequence of the concomitant decrease in K<sub>f</sub> as seen in Figure 2.

A fall in the production of renal vasodilators such as nitric oxide is suggested by the marked decrease in urinary nitrites/nitrates during the Ang II infusion, which also contributes to the renal vasoconstriction. Consistent with the reduction of urinary nitrites, it has been reported that the infusion of Ang II results in an attenuated immunostaining of nitric oxide synthase 1 (NOS1) in the macula densa and of NOS 3 in the outer and inner medulla (Lombardi et al., 1999).

In addition, a marked structural injury is associated to the Ang II-induced hypertension that may be responsible for the alteration of renal hemodynamics; proliferation of smooth muscle cells with an increased thickness of the afferent arteriole is observed. Even if these alterations are common findings in hypertension, Ang II also induces smooth muscle

proliferation by itself. However, the most important renal alterations induced by Ang II are the increase of smooth muscle  $\alpha$ -actin expression by mesangial cells in spite of minimal glomerular cell proliferation, a tubulointerstitial damage characterized by myofibroblasts adjacent to the peritubular capillary network, fibrosis by focal deposition of collagen type IV, as well as an infiltration of monocytes and interstitial deposit of osteopontin (Johnson et al., 1992). A minimal focal tubular cells injury and proliferation, was also observed (Johnson et al., 1992; Ozawa et al., 2007).

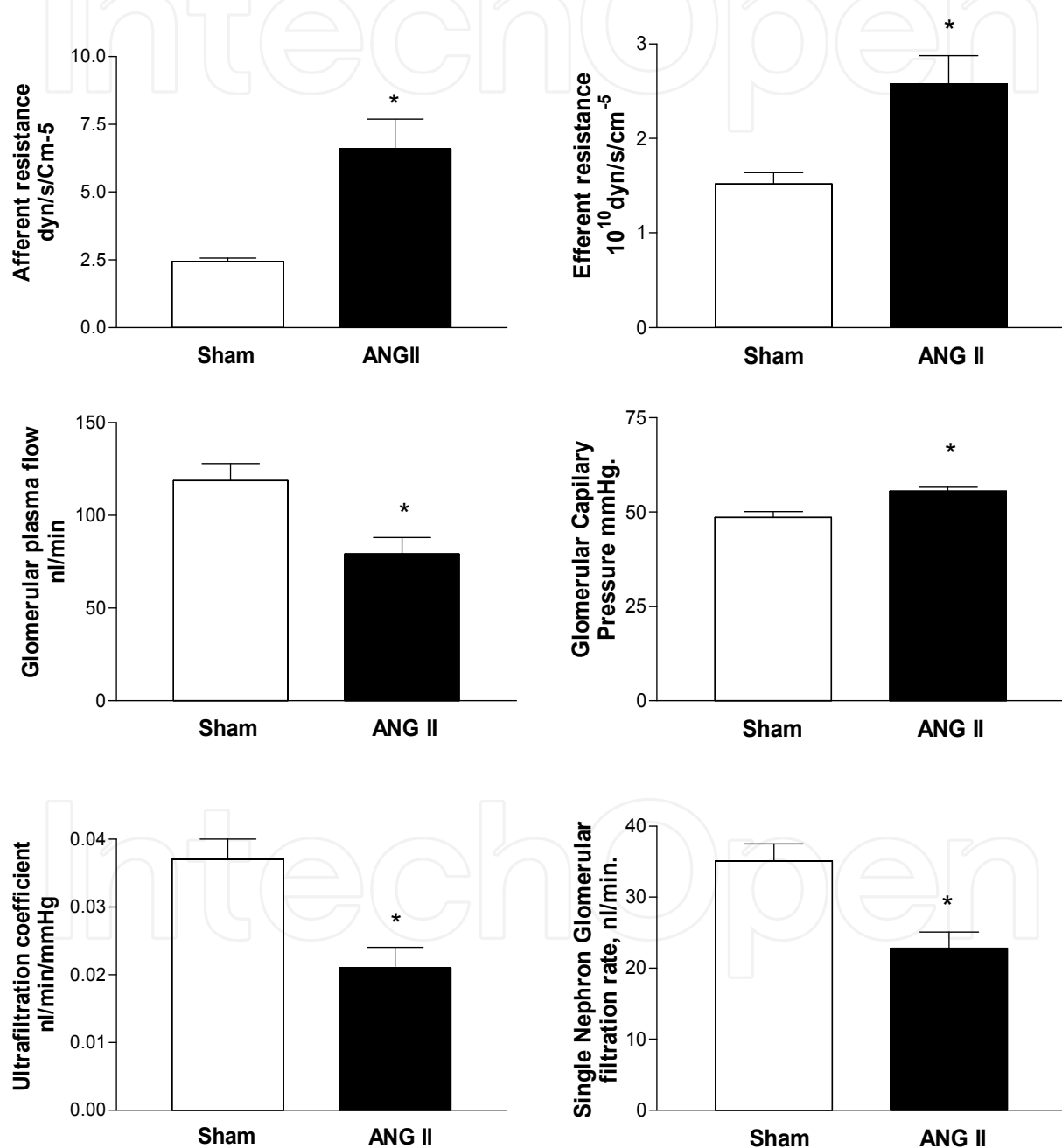


Fig. 2. Glomerular hemodynamics in Sham and Ang II hypertensive rats. The effects of angiotensin are shown in afferent and efferent resistances, glomerular plasma flow, glomerular capillary pressure, ultrafiltration coefficient and single nephron glomerular filtration rate (modified from Franco et al. 2001).

In this regard, relevant importance has been attributed to the production of cytokines, growth factors and angiotensin II produced by the interstitial inflammatory cells, that enhances intrarenal Ang II and induces renal cortical vasoconstriction (Rodriguez-Iturbe et al., 2001; Suzuki et al., 2003; Ruiz-Ortega et al., 2003; Franco et al., 2006). In addition to the direct effects of Ang II on the renal microcirculation, several vasoactive compounds appear to contribute to elevate the renal vascular resistance, including endothelin, 20-HETE and asymmetric dimethyl arginine, as well as ATP and adenosine (Sasser et al., 2002; Lai et al., 2009).

### **3. Participation of adenosine receptors in the renal vasoconstriction of Ang II-infused hypertensive rat**

Several conditions that induce the elevation of Ang II concentrations also enhance the vasoconstrictor response of the kidney to adenosine (Hall & Granger, 1986; Hansen et al., 2003; Weihprecht et al., 1994; Nishiyama et al., 2001). Furthermore, various studies suggest that Ang II-induced ischemia results in the *de novo* formation of adenosine. In this context, an important factor to take in consideration is that adenosine is a vasoactive metabolite of ATP, and the elevation of blood pressure by Ang II results in a high interstitial renal concentrations of ATP.

The synergic interaction between Ang II and adenosine to induce renal vasoconstriction is well recognized (Hall et al., 1985; Weihprecht et al., 1994) and it is essential in the regulation of renal hemodynamics and tubuloglomerular feedback (Osswald et al., 1977). Nevertheless, the mechanisms involved in such synergic interaction have not been completely elucidated; several studies suggest that under acute changes in the concentration of the corresponding agonists, the degree of activation of Ang II AT1 or adenosine A1 receptors determines the magnitude of the constrictor response of the renal vasculature (Weihprecht et al., 1994). Furthermore, the synergism seems partially mediated by A1 receptors, since in the adenosine A1 knockout mice AT1 and A2a receptors remained unchanged, but the vascular response to Ang II in the kidney was diminished (Hansen et al., 2003). Taking into account that the local renal adenosine concentrations could be the factor that contributes to the interaction with Ang II (Franco et al., 2008), we measured the interstitial adenosine concentrations in the cortex of sham-control and Ang II-treated rats. Ang II doses were 435, 260 or 130 ng/kg/min, and as observed in Figure 3, only the higher dose significantly increased both tissue content and interstitial concentrations. It has been proposed that the renal vasoconstriction and reduced glomerular filtration rate observed in the Ang II model results from a fall in glomerular plasma flow and K<sub>f</sub> (Franco et al., 2008), as a consequence of the Ang II administration. Indeed, our results obtained in the micropuncture experiments clearly demonstrate the vasoconstriction after 14 days of infusion with Ang II. In this regard, Zou et al. (Zou et al., 1996) demonstrated that after 14 days of treatment, Ang II was elevated in the kidney; the renal concentration of Ang II may be attributed to the accumulation of the exogenous peptide, but endogenous angiotensin was also elevated. Since adenosine content and interstitial concentration of adenosine are elevated, the interaction between both vasoactive compounds is certain. In addition, when we infused the specific A1 adenosine receptor blocker DPCPX, the blood pressure remained unchanged, and the renal hemodynamic alterations induced by Ang II were completely reversed. Under

these conditions, only the glomerular capillary pressure remained elevated, suggesting an impairment of autoregulation, which allowed the transmission of the systemic pressure to the glomeruli (Figure 4). These experiments demonstrate the contribution of adenosine receptor in the renal vasoconstriction by temporal infusion of Ang II.

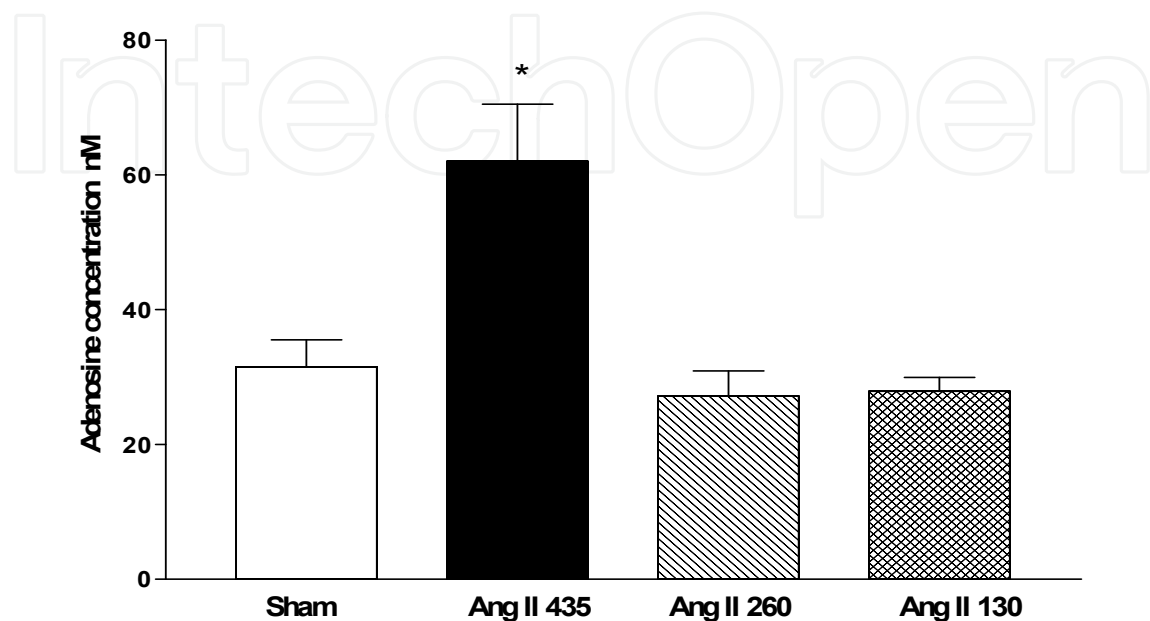


Fig. 3. Interstitial adenosine concentration in the renal cortex of Sham and Ang II-treated rats Ang II doses were 435, 260 or 130  $\text{ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  \*  $p < 0,001$  vs. Sham, and vs. Ang II 260 and 130  $\text{ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , (modified from Franco et al. 2008).

To evaluate the mechanism involved in the increased concentration of adenosine in the kidney of Ang II hypertensive rats, we evaluated the enzymes involved in the metabolism of adenosine. On one hand, the 5'-nucleotidase catalyzes the conversion of adenine nucleotides to adenosine in the extracellular compartment from renal sympathetic nerve terminals, renal endothelial cells, renal vascular smooth muscle cells and/or epithelial cells (Gordon et al., 1989; Jackson et al., 2007). On the other hand, adenosine deaminase is responsible of the degradation of ADO to inosine, which has not vasoactive properties. When the activities of 5'-nucleotidase and adenosine deaminase were investigated, the enzyme located at cytosol as well as that on the membrane were separated to evaluate the participation of both fractions. Despite the lack of changes of 5'-nucleotidase activity, adenosine deaminase activity was significantly higher in the membrane fraction from the Sham-control group that in those from the Ang II-treated rats, without changes in the cytosol fraction (Figure 5).

Despite a lack of changes in the cytosolic and membrane activity of the 5'-nucleotidase between control and Ang II groups, the adenosine deaminase activity was decreased in the Ang II group; these changes were associated to a decrease in protein and mRNA levels of adenosine deaminase.

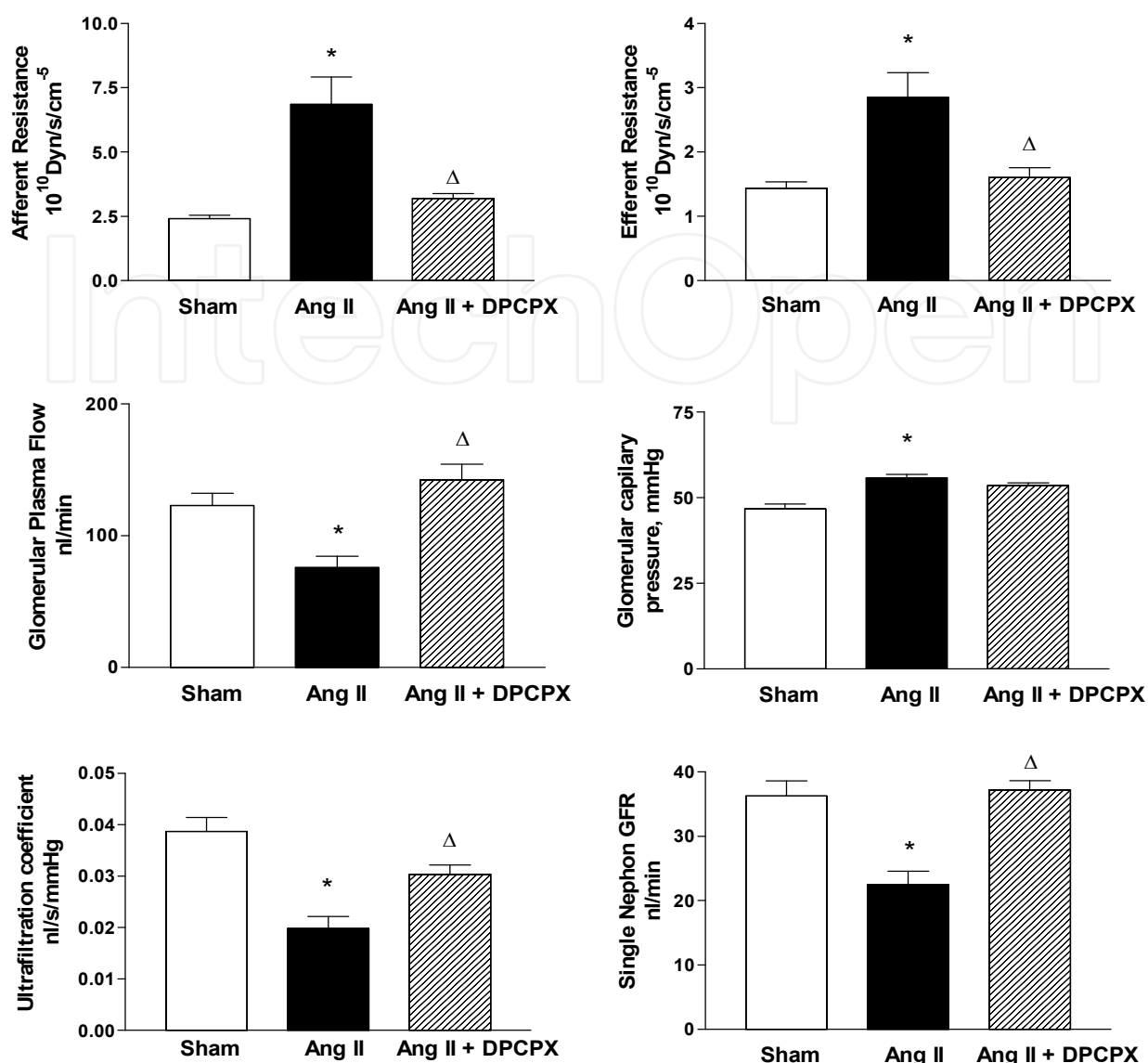


Fig. 4. Afferent and efferent resistances, glomerular plasma flow, glomerular capillary pressure, ultrafiltration coefficient and single nephron GFR in Sham, Ang II hypertensive rats and Ang II with infusion of the adenosine A1 blocker DPCPX. \* $p < 0.01$  vs. Sham;  $\Delta p < 0.01$  vs. Ang II, (modified from Franco et al. 2008).

These data are in agreement with the adenosine concentration found in the tissue and with microdialysis determinations in Ang II treated animals (Franco et al., 2008). In addition, since ecto- and intracellular enzymes were separated in this study, the changes in the ecto-adenosine deaminase suggest that the increase of interstitial adenosine concentrations could be attained through both, the decreased activity of ecto-adenosine deaminase, and an increased production of adenosine. In this regard, studies by Dietrich et al., (Dietrich et al., 1991) have demonstrated that adenosine can be synthesized in the extracellular compartment through the breakdown of ATP. The ATP is released from circulating erythrocytes when luminal partial pressure of O<sub>2</sub> falls in the arterioles, as happens in the Ang II-mediated hypertensive model (Welch et al., 2005). Moreover, microvascular endothelial cells and basolateral membranes from the proximal tubule have



high activity of extracellular ecto-nucleotidase, which degrades adenine nucleotides to adenosine (Jackson et al., 2001; Jackson et al., 2007). The adenosine increase in renal tissue observed in the Ang II-induced hypertension is probably the result of a significant increase of local nucleotidase, and a reduction of ecto-adenosine deaminase (Franco et al., 2008).

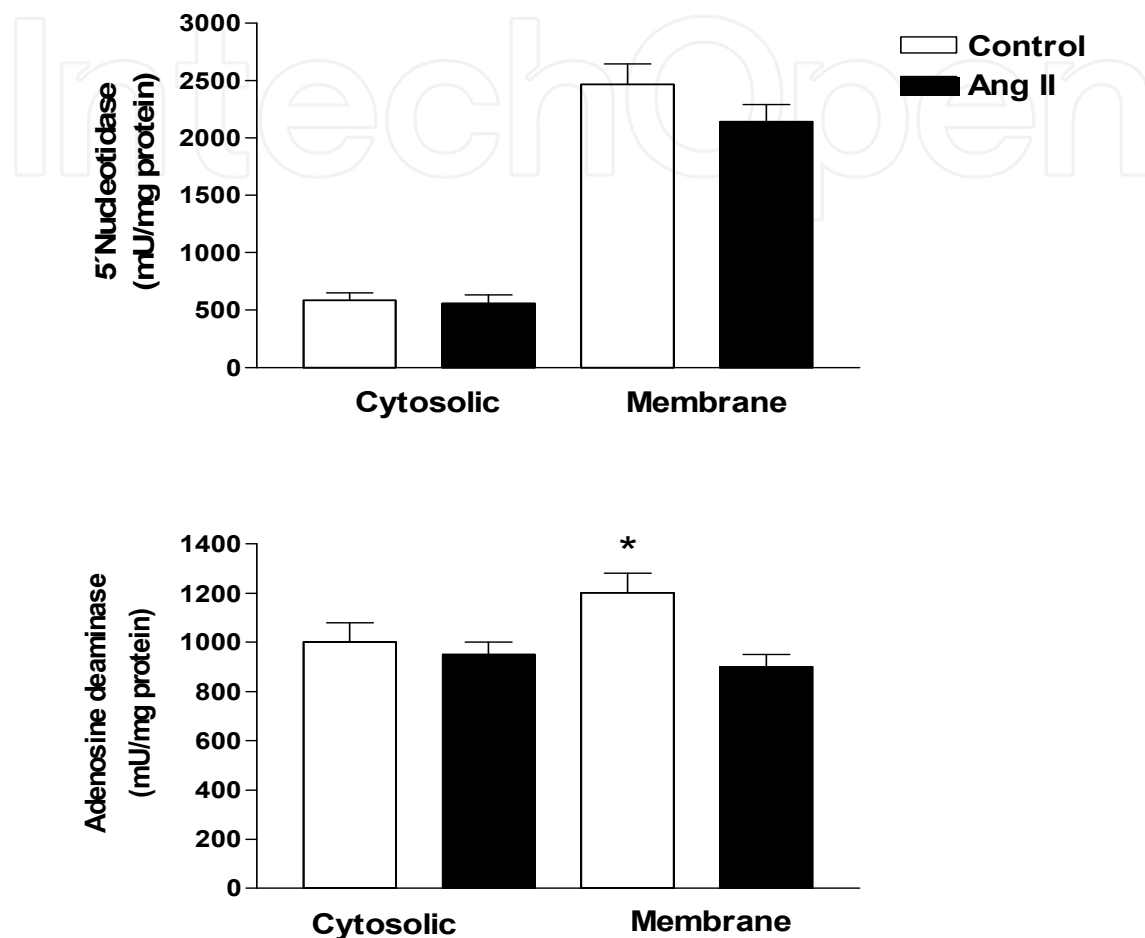


Fig. 5. 5' nucleotidase and adenosine deaminase activities in cytosolic and membrane fractions from control and Ang II treated rats. \* $p < 0.05$  vs. cytosolic fraction (modified from Franco et al. 2008).

Furthermore, the adenosine receptor expression was modified in the Ang II hypertensive rat; in this model, it was observed an imbalance between the receptors that mediate vasoconstriction (A1) and vasodilation (A2) that could influence the renal Ang II-mediated vasoconstriction. When adenosine receptors were evaluated, the A1 receptors protein did not change significantly in either the cortex or the medulla, indicating a lack of regulation by the high adenosine concentrations (Franco et al., 2008), which has not been observed with an acute infusion of Ang II; the adaptation of adenosine receptors to chronic exposure to the agonist remains to be determined. In this regard, the A1 receptor require up to 6 days in rat adipocytes for desensitization, (Palmer & Stiles, 1997), and a slight but significant decrease in the high affinity A2a receptor and no change in the low affinity A2b receptors were observed, indicating down regulation of the former (Figure 6).

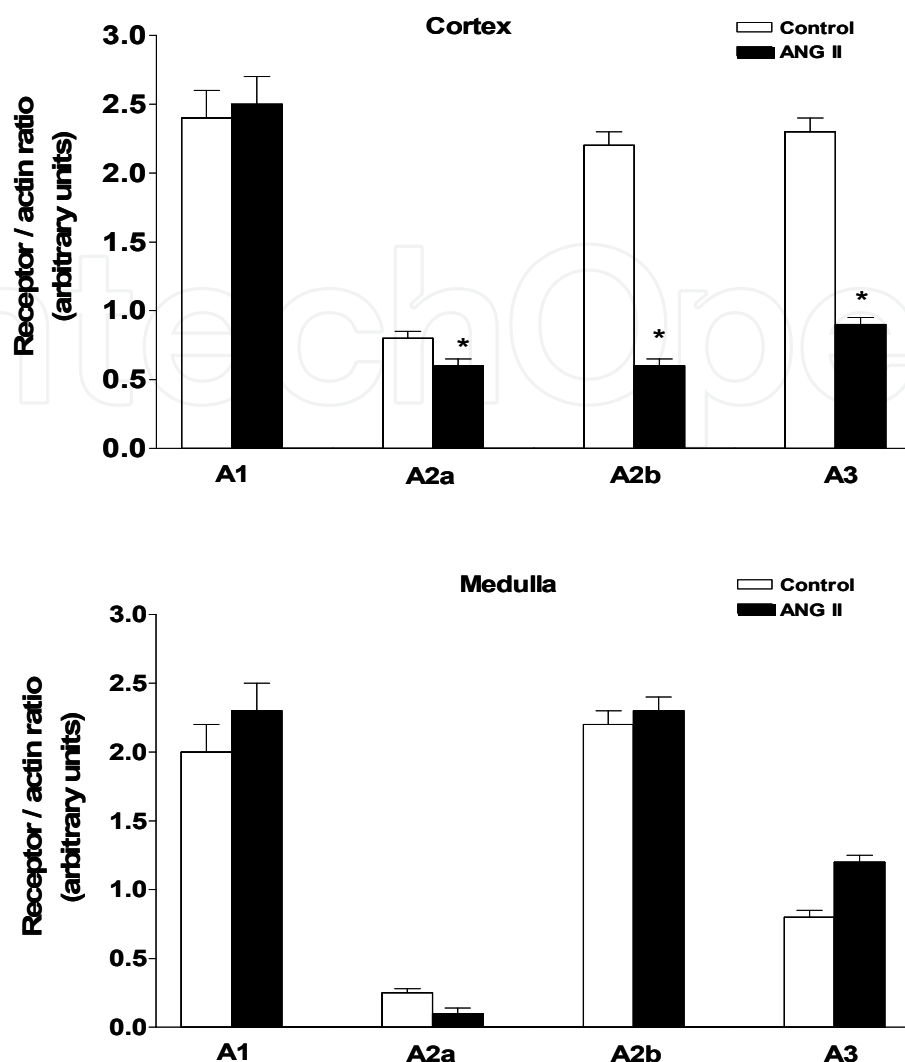


Fig. 6. Adenosine receptor protein expression in renal cortex (top) and medulla (bottom) from control and Ang II treated rats. \* $p < 0.05$  vs. control rats (modified from Franco et al. 2008).

This finding is in agreement with the fast response of A2a receptors to high levels of adenosine acutely administered (Palmer & Stiles, 1997). Normal expression of A1 receptors population with a decrease in A2a receptors, associated to an elevated concentration of adenosine, may explain synergic effect of adenosine to Ang II-induced renal vasoconstriction (Franco et al., 2001). This notion was further supported by the results obtained in the micropuncture studies; the acute blockade of A1 receptors with the intra-aortic administration of the specific A1 antagonist DPCPX completely reverted the renal vasoconstriction induced by Ang II. These unexpected results clearly demonstrate the great contribution of adenosine in the renal vasoconstriction of the Ang II-infused hypertensive rat. We can attribute the vasodilatory effect of the blocker to an overriding effect of A2 receptors; the reason for this marked vasodilatory response to the specific adenosine A1 antagonist remains to be elucidated.

We also demonstrated an increase in the expression of A3 receptors (Franco et al 2008). In this regard, the physiological effect of A3 receptors in the kidney remains unclear. However, up regulation of these receptors has been associated with deleterious effects in renal

function in the renal ischemia-reperfusion model (Lee et al., 2003). In the Ang II-mediated hypertensive model, they could have a similar effect, since ischemia has also been observed (Welch et al., 2005)

#### 4. Participation of ATP to the renal vasoconstriction of the Ang II-infused hypertensive rat

As mentioned above, chronic Ang II infusion lead to a progressive increase in arterial pressure associated with renal vasoconstriction thus maintaining at low levels the renal blood flow and the glomerular filtration rate. Since high arterial pressure result in elevated interstitial levels of ATP in the kidney, which contribute to the autoregulatory-associated responses in microvascular resistances, it is suitable to consider that some of the elevation in vascular resistances observed in Ang II-induced hypertension is modulated by purinergic receptors (Franco et al., 2008). Furthermore, ATP participates in the regulation of vascular resistance and is elevated in Ang II-induced hypertension (Graciano et al., 2008). These observations suggest a modulatory role of ATP in the renal vasoconstriction induced by temporal administration of Ang II. Thus, we explored the possible contribution of ATP

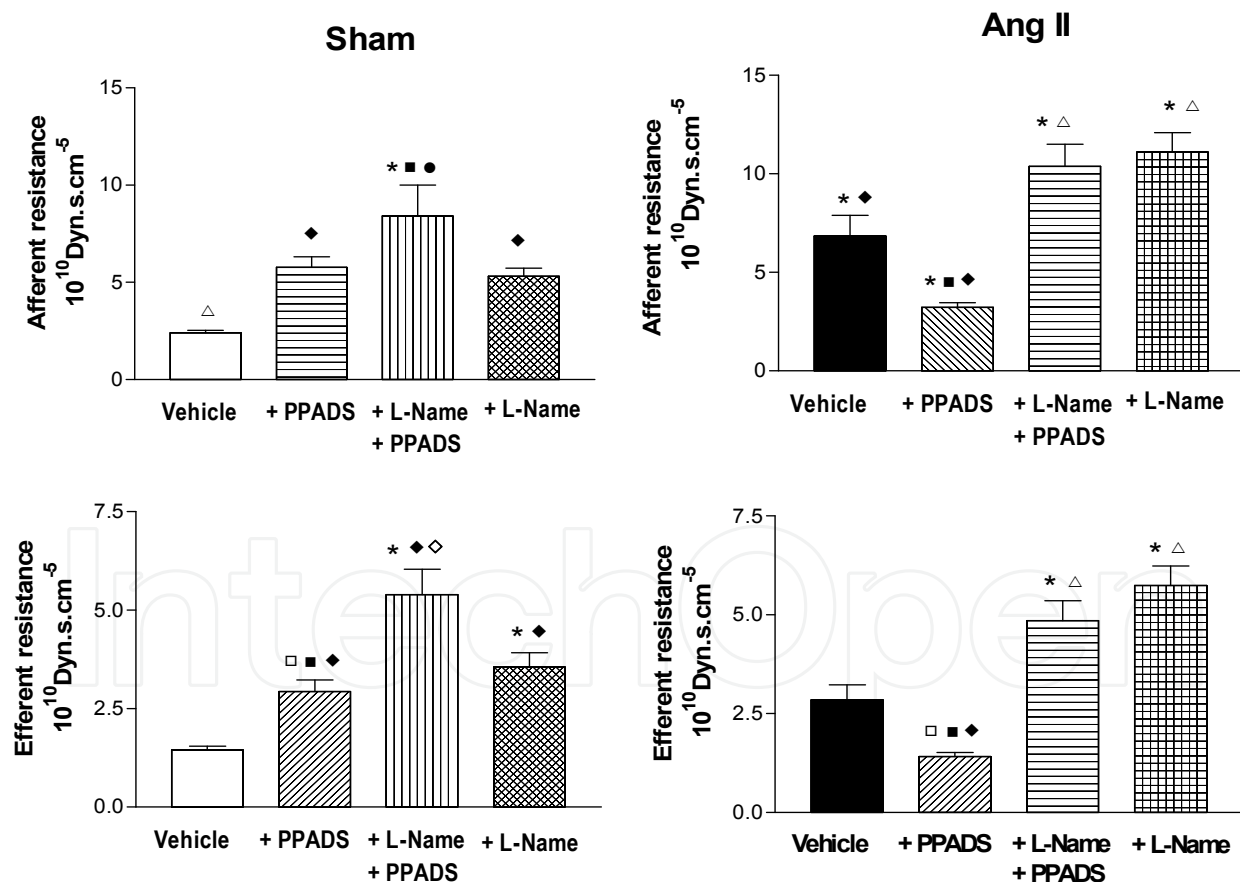


Fig. 7. Afferent and efferent resistances in Sham-control and Ang II groups at baseline, during the administration of PPADS, and the co-administration of L-NAME+PPADS and L-Name alone. \*  $p < 0.001$  vs. Sham-vehicle;  $\Delta$   $p < 0.01$  vs. Ang II+vehicle;  $\diamond$   $p < 0.01$  vs. Sham+L-NAME;  $\blacksquare$   $p < 0.001$  vs. Ang II+PPADS;  $\bullet$   $p < 0.01$  vs. Ang II+PPADS+L-NAME;  $\blacklozenge$   $p < 0.01$  vs. Ang II+L-NAME (modified from Franco et al. 2011)

purinergic receptors in the renal hemodynamics and glomerular alterations observed in the Ang II-mediated hypertension in rats. Ang II-induced renal vasoconstriction, on the acute administration of PPADS, (a P2X and P2Y antagonist), reduced afferent and efferent resistances, restoring glomerular blood flow and single nephron glomerular filtration rate (Figures 7 and 8).

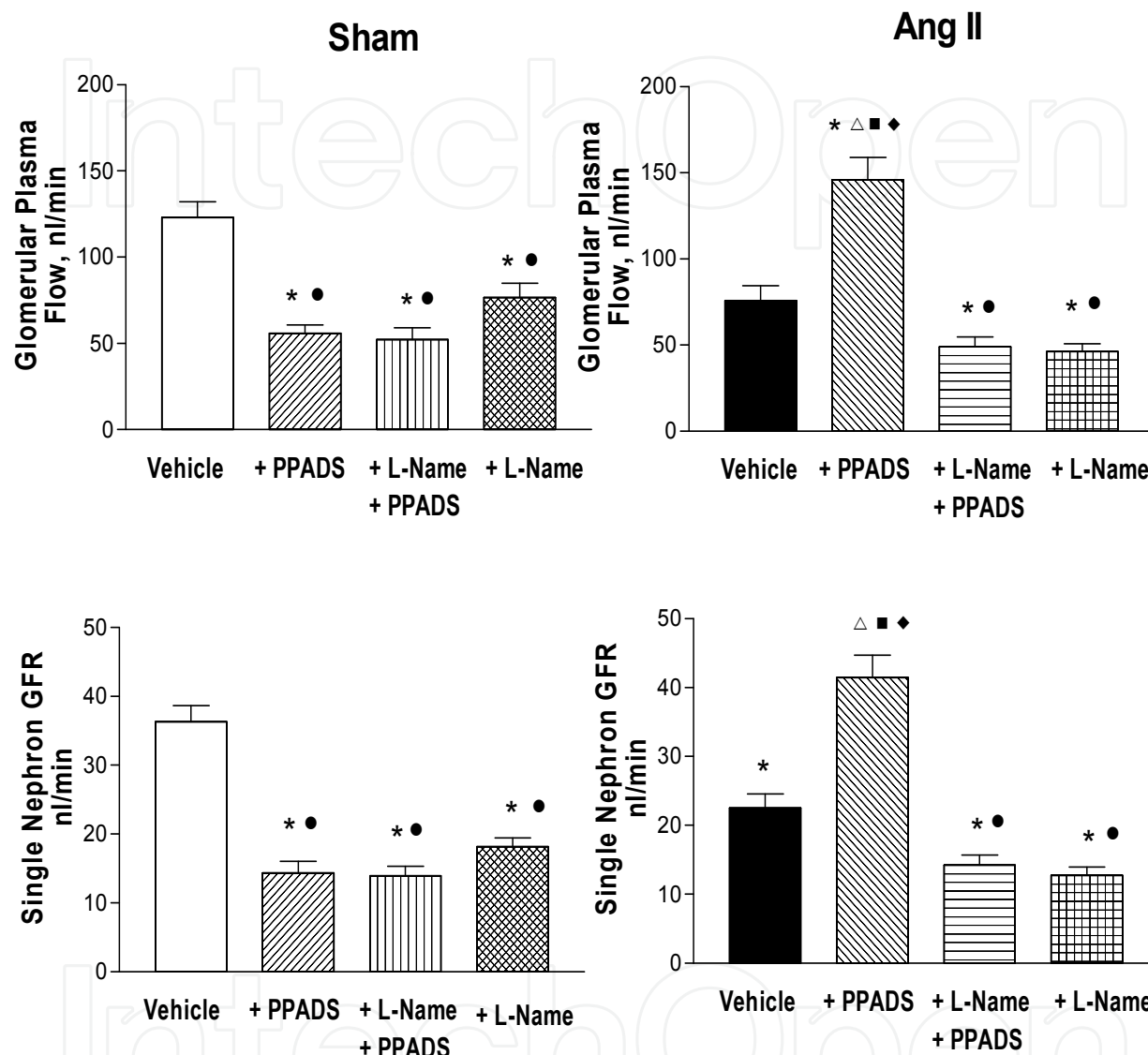


Fig. 8. Glomerular plasma flow and single nephron GFR, in Sham-control and Ang II groups at baseline, during the administration of PPADS, and the co-administration of L-NAME+PPADS and L-NAME alone. \* $p < 0.001$  vs. Sham-vehicle;  $\Delta$   $p < 0.01$  vs. Ang II+vehicle;  $\blacksquare$   $p < 0.001$  vs. Ang II+PPADS;  $\bullet$   $p < 0.01$  vs. Ang II+PPADS+L-NAME (modified from Franco et al. 2011).

These changes in glomerular hemodynamics cannot be attributed to modifications in blood pressure, since PPADS did not ameliorate the elevated blood pressure neither in the Ang II group, nor the Sham group. These findings suggest an important contribution of ATP in mediating the renal vasoconstriction via activation of P2 purinergic receptors. Interestingly, P2X and P2Y receptors are expressed primarily in afferent but not in efferent arterioles; therefore, the effects of PPADS on efferent arterioles suggest the presence of additional

systems that become activated after purinergic blockade in the Ang II-infused rats (Chan et al., 1998; Ichihara et al., 1998; Lambrecht, 2000; Lewis & Evans, 2001; Turner et al., 2003). In addition, P2X1 and P2Y1 receptors expression in the cortex of Ang II rats was significantly higher on the immunohistochemical studies (Figure 9).

Several mechanisms may be involved in the renal vasodilation induced by PPADS; P2X1 receptors were upregulated in the cortical tissue of the Ang II group. Therefore, the increased number of these receptors may have been exerting a direct effect on the vascular smooth muscle to increase renal vascular resistance, and their blockade induces vasodilation. It is possible that P2X1 blockade unmask the influence of P2Y receptors as P2y2, P2y4, P2Y6 and P2Y12, which are not blocked by PPADS (Lambrecht, 2000), and those P2Y receptors may exert vasodilatory effects on the smooth muscle cells via release of NO by the endothelial cells, thus helping to explain the decrease in efferent resistance (Jackson, et al, 2007) as shown in figure 7 (Franco, 2008), in which the blockade of NO with L-NAME prevents the vasodilator effect of PPADS (Lambrecht, 1996; Lambrecht, 2000). In this regard, P2X4 receptors have been described in endothelial cells, and they induce NO release (Burnstock, 2006; Jones et al., 2000). However, the activation of P2X1 receptors also stimulates p-450 pathway and induces production of the vasoconstrictor HETE (Zhao et al, 2001) and this mechanism may be blocked by PPADS, resulting in vasodilation. In addition, PPADS increased NO productions, which also inhibit HETE synthesis (Oyekan & McGiff, 2002); thus, both mechanisms (which occurred simultaneously) may explain the vasodilation observed in the Ang II rats.

Since purinergic blockade may modify the release of NO production, further studies were performed to investigate the role of NO in the response to PPADS. Importantly, using the urinary excretion of nitrites ( $\text{UNO}_2^-/\text{NO}_3^-$ ) as a marker of NO activity, we found that it was low in the Ang II-infused rats compared with Sham rats at baseline, but increased greatly with the infusion of PPADS (Franco et al 2011). These results suggesting that NO produced by the endothelial cells was directly stimulated by PPADS, or maybe through an effect on P2Y or P2X receptors not blocked by PPADS to release NO and elicit vasodilation (Figure 10).

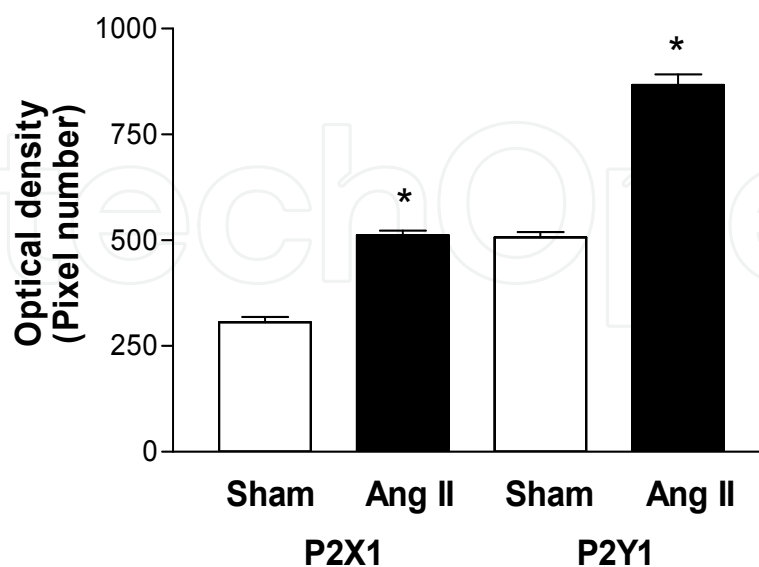


Fig. 9. P2X1 and P2Y1 immunostaining evaluated by morphometric analysis (expressed as pixel number) in the cortex of Sham-control and Ang II treated rats.\*  $p < 0.0001$  vs. Sham (modified from Franco et al. 2011)

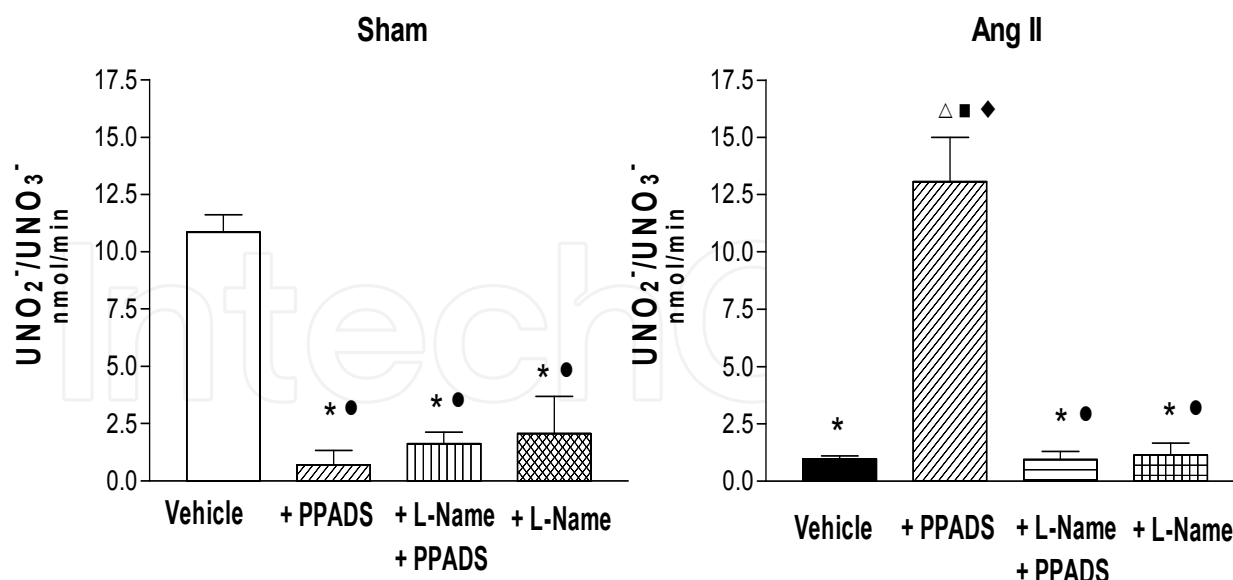


Fig. 10. Urinary excretion of nitrites/ nitrates ( $\text{UNO}_2^-/\text{NO}_3^-$ ) from Sham-control and Ang II groups at baseline, during PPADS and coadministration of L-NAME+PPADS, and L-NAME alone. \*  $p < 0.001$  vs. Sham-vehicle;  $\Delta$   $p < 0.01$  vs. Ang II+ vehicle;  $\bullet$   $p < 0.001$  vs. Ang II+PPADS;  $\blacksquare$   $p < 0.001$  vs. Ang II+L-NAME +PPADS;  $\blacklozenge$   $p < 0.01$  vs. Ang II+L-NAME (modified from Franco et al. 2011)

This finding was supported by the results observed upon co-administration of PPADS and L-NAME, which returned  $\text{NO}_2^-/\text{NO}_3^-$  urinary levels to those found at baseline, thus suggesting the existence of NO-mediated dilation in the PPADS group (Franco et al. 2011). In our study this possibility is further supported by the fact that blockade of NO with L-NAME alone elicited effects similar to those obtained with PPADS+L-NAME (Franco et al. 2011). In this regard, it is recognized that activation of P2Y receptors induces release of ATP by shear stress in the endothelial cells, through an increase on intracellular calcium, which activates NOS and NO production in the endothelium (Buvinic et al., 2002).

In a study, a low NO can explain the efferent vasoconstriction, which returned to near-normal values when NO increased in response to PPADS (Inscho et al., 1992). In addition, although PPADS is a non-selective P2 receptor antagonist, it is very specific for purinergic receptors (Windscheif et al., 1994), it also blocks ecto-ATPasas (Chen et al., 1996; Lambrecht, 2000) and it may not block P2Y2 and P2Y12 receptors (Lambrecht, 1996; Lambrecht, 2000; Rost et al., 2002). It should be noticed that in the Sham rats PPADS induced a paradoxical renal vasoconstriction, as manifested by an increase in afferent and efferent resistance, and a reduction in glomerular blood flow, SNGFR and  $K_f$ . These responses indicate that the effects of P2 receptors in normal control rats are primarily vasodilator and can be attributed to the existence of a P2 receptor population in the endothelium, linked to NO release in the kidneys of Sham rats. Thus, it is possible that the renal vasoconstriction in this group may be due to blockade of P2Y1 or P2X4 receptors on the endothelial cells (Chen et al., 1996; Boyer et al., 1994; Curchill & Ellis, 1993). As above-mentioned, it has been demonstrated that P2X4 receptors are located in the endothelial cells and are linked to NO release, leading to vasodilation in dome vessels (Burnstock, 2006; Lewis, 2001; Yamamoto, 2006). Thus the blockade of P2X4 receptors by high concentrations of PPADS would decrease NO production and induce vasoconstriction (Jones et al. 2000) and could explain the findings

that the efferent as well the afferent arteriolar resistances were reduced. Under these conditions, the co-administration of PPADS with L-NAME was not expected to have a much greater additional effect, which was the case in the Sham rats. However, we cannot rule out that, in the presence of NO blockade the effect of endogenous vasoconstrictor mediators could be enhanced and alter renal function. It is recognized that the renal vasoconstriction observed in the Sham rats with PPADS (Franco et al. 2011) was not observed by Tanaka et al (Takenaka et al., 2008) or Osmond and Inscho (Osmond & Inscho, 2010); these authors used an intravenous bolus, each 20 min with a lower dose than ours. Under those conditions, lower concentrations of PPADS possible reach the kidney; however the dose used in those studies (Osmond & Inscho, 2010) were sufficient to block P2 receptors as evidenced by the blockade of the vasoconstrictor response to  $\alpha,\beta$ methylene ATP; thus an explanation for the divergent effects of PPADS in Sham rats remains to be elucidated.

We also observed that sodium excretion was increased by PPADS in both Sham and Ang II-infused rats, suggesting that the increase P2 receptor activity inhibits tubular reabsorption. These data are similar to those found in rats receiving a low salt diet (Dobrowolski et al., 2007). The co-administration of L-NAME further increases sodium elimination, but inhibits NO excretion; however, the increase in sodium excretion induced by L-NAME alone was lower, than the Ang II group indicating that NO partially mediated the increase in sodium excretion. It should be mentioned, that the increase in sodium excretion, mainly in the Ang II group, was associated with a marked decrease in the urinary excretion of  $\text{NO}_2^-/\text{NO}_3^-$  indicating that the  $\text{NO}_2^-/\text{NO}_3^-$  is a specific marker of renal NO production in this model and it is not the result of nonspecific increased urinary sodium excretion.

These results indicate that temporal Ang II infusion up-regulates P2X1 receptors, which may contribute to increases the renal cortical vascular resistance observed in the Ang II-dependent hypertension. The results also indicate that in Ang II-infused rats PPADS may elicit a marked stimulation of NO, which may also contribute the reduced afferent and efferent arteriolar resistance.

## 5. Conclusions

The renal vasoconstriction induced by chronic administration of angiotensin II is complex, since several vasoactive compounds contribute to the abnormalities induced by the peptide in the renal glomerular hemodynamics. The results obtained in our studies indicate that the temporal infusion of Ang II, produces elevation of renal tissue content and interstitial concentration of adenosine which contributes to the renal vasoconstriction observed in this model. Our studies suggest that the mechanism by which Ang II increases adenosine production is through the extracellular nucleotide degradation of ATP, as well as a decrease of ecto-ADA, that impairs adenosine degradation; the elevated adenosine thus induce an imbalance in A1 and A2 receptors. Since the ATP seems to be related in a very important manner with the results obtained in our first study, we further investigated the participation of ATP in the renal vasoconstriction observed during the chronic infusion of angiotensin II. We found that Ang II regulates P2X1 receptors, and contributes to increase the renal vascular resistance observed in the ANG II-dependent hypertension. Under these conditions PPADS, a non selective ATP receptors blocker (P2X and P2Y receptors) elicit a marked stimulation of NO production which contributes to reduce afferent and efferent arteriolar resistances, normalizes the glomerular blood flow and the ultrafiltration coefficient,

resulting in a normalization of the single glomerular filtration rate and renal function return to normal values. Thus, elevation of ATP and adenosine contributes to the alteration in renal hemodynamics in the Ang II-induced hypertension.

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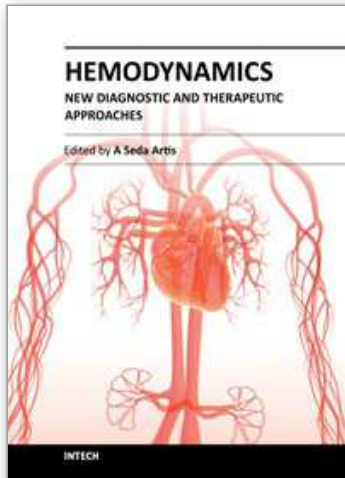
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