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Vasoactive peptide receptors in the rat kidney

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The kidney is composed of different complex structures regulating –among others– renal blood flow and glomerular filtration rate. Several vasoactive peptide systems are involved in that regulation, including atrial natriuretic peptides, the renin-angiotensin system, endothelin and their respective receptors. In this review, we will briefly describe the characteristics, location and regulation of these receptors in the rat kidney.

Key terms: *atrial natriuretic peptides, endothelin, kidney, rat, renin-angiotensin system, vasoactive peptide receptors*

ATRIAL NATRIURETIC PEPTIDES

The atrial natriuretic factor (ANF) evokes a variety of physiological responses through its interaction with specific receptor in target tissues. Two other members of the natriuretic peptide family, brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) have been also identified. All three peptides (ANF, BNP and CNP) show a high sequence homology, although CNP lacks the C-terminal tail found in ANF and BNP (Brochner-Mortensen & Ditzel, 1982; Mogensen, 1971).

The biological effects of natriuretic peptides are mediated by two classes of receptors, namely guanylate cyclase containing receptors, with cGMP as the intracellular messenger, and non-guanylate cyclase containing receptors. The latter has been named NPR-C and it has been postulated as a clearance receptor and to inhibit adenylate cyclase (Anand-Srivastava & Trachte, 1993; Drewett & Garbers, 1994). Guanylate cyclase-coupled receptors can be distinguished as NPR-A and NPR-B. All three receptors have been cloned (Drewett & Garbers, 1994; Silver *et al*, 1992). Both NPR-A and NPR-B receptors have an extracellular binding domain, a short transmembrane region and a catalytic guanylate cyclase domain. In NPR-C, the intracellular domain is replaced by a short-tail. There is an identity of 43% for the extracellular domain and 78% for the intracellular region between NPR-A and NPR-B. The apparent extracellular binding domain for NPR-A and NPR-B has a 80-85% identity. The extracellular region of NPR-A and NPR-B is 33% and 29% respectively, identical to the extracellular region of NPR-C (Drewett & Garbers, 1994; Silver *et al*, 1992). The NPR-A and NPR-B receptors have conservative structural requirements and they will not bind several truncated analogs such as des [Glyn^{18}, Ser^{19}, Gly^{20}, Leu^{21}, Gly^{22}] ANF (Koller *et al*, 1991; Anand-Srivastava *et al*, 1984), C-ANF, which, however, binds NPR-C receptor with high affinity (Karibe *et al*, 1991). The NPR-A receptor has a slightly higher affinity for ANF than for BNP, both of which also bind NPR-C with high affinity (Silver *et al*, 1992). The C-type natriuretic peptide has been reported as the specific ligand for NPR-B, but also

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binds C-type receptor with high affinity (Silver *et al*, 1992).

The study of tissue distribution and regulation of NPR-A and NPR-B receptor proteins have been hampered by the unavailability of selective agonists or antagonists. Furthermore, a second shorter non-functional form of NPR-B mRNA produced by alternative splicing, has been reported in rat brain and kidney (Craven & DeRubertis, 1989; Bianchi *et al*, 1986). Both isoforms have the same affinity for CNP, but since the second form lacks the nucleotides corresponding to the head of the protein kinase-like domain, no cGMP is produced upon stimulation (Craven & DeRubertis, 1989). The ANF receptors have been found in the kidney (Ballerman *et al*, 1985; Gauquelin *et al*, 1987), blood vessels (Schiffrin *et al*, 1985) and other target organs (Bianchi *et al*, 1985). In the kidney, high (NPR-A and NPR-B) and low (NPR-C) molecular weight receptors are expressed in glomeruli, in glomerular microvessels and papillae (Bianchi *et al*, 1985; Brown *et al*, 1990; de Leon *et al*, 1993), but only the high molecular weight is expressed in papillae (Martin *et al*, 1989). We have reported the presence of NPR-A and NPR-C subtypes in glomeruli and only NPR-A in papillae, but no NPR-B was detected (de Leon *et al*, 1994). However, NPR-B mRNA has been reported in human and rat kidneys (Stingo *et al*, 1992; Terada *et al*, 1994). In the latter, the PCR product of NPR-B was present in glomeruli, vasa recta bundle arcuate artery and distal nephrons (Terada *et al*, 1994).

The expression of the NPR-B receptor protein is under dispute. Ligand binding experiments performed in our (de Leon *et al*, 1994) and other laboratories (Brown & Zno, 1992, 1994; Luk *et al*, 1994) have not detected NPR-B on any rat or hamster renal structures. Using anti-NPR-B specific antibodies, the presence of NPR-B has been reported in rat renal glomeruli, cortical collecting tubules and the apical pole of the medullary collecting ducts, but not in renal vasculature (Dean *et al*, 1996; Ritter *et al*, 1995). Using antibodies raised against a 15-mer synthetic peptide representing an epitope NPR-B extracellular domain, we have found recently (Fig 1) that in the rat kidney NPR-B is present exclusively in the glomerular tuft and renal microvessels. No NPR-B was detected in tubular segments. This distribution agrees with the predominant vascular (Stingo *et al*, 1992) over the renal (Tawaragi *et al*, 1991) effect of CNP. Contrariwise to glomeruli, rat renal preglomerular microvessels have a large predominance of type A over type C receptors (de Leon *et al*, 1993, 1994) and reported to be reciprocally regulated by plasma ANF levels (Ballerman *et al*, 1985, 1986; Gauquelin *et al*, 1987; Garcia *et al*, 1988). However, several findings suggest that plasma ANF levels may not be the only factor involved on ANF receptor regulation since ANF receptors may be either up or down regulated, or unchanged, depending on tissue localization (Cachofeiro *et al*, 1990; Garcia *et al*, 1992). Whether NPR-A and NPR-B subtypes are differently or similarly regulated, is not known.

RENIN-ANGIOTENSIN SYSTEM (RAS)

The RAS plays a pivotal role in sodium and water homeostasis and blood pressure regulation through the production of angiotensin II (ANG II). Angiotensin II specific binding sites have been localized by *in vitro* autoradiography and they have been correlated to change in physiological function (Gehlert *et al*, 1991; Mendelsohn *et al*, 1987). Thus ANG II increases peripheral vascular resistance and reduces renal excretion of Na^+ directly augmenting $NaHCO_3$ renal reabsorption in the proximal tubule, or indirectly on aldosterone mediated Na^+ renal reabsorption (Liu & Cogan, 1989). Angiotensin II increases renal vascular resistance by constricting the afferent arteriole and the interlobar, arcuate and interlobular arteries (Boknam *et al*, 1981; Källskog *et al*, 1976), suggesting an important contribution of the preglomerular vessels in the regulation of cortical blood flow. High affinity ANG II receptors have been identified in glomeruli, renal medulla, brush border of the basolateral membranes and preglomerular vessels (Sraer *et al*, 1974; Mendelsohn *et al*, 1986; Brown &

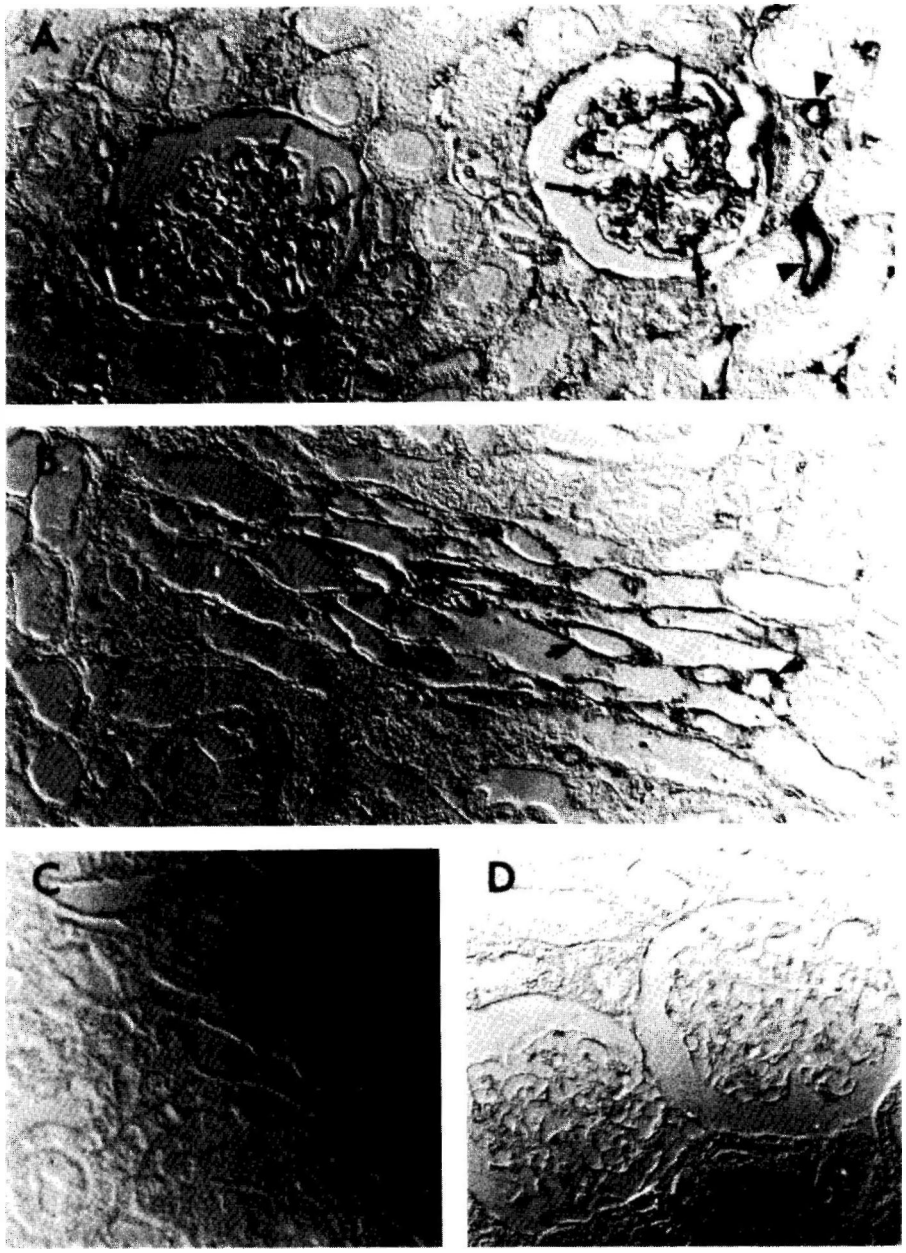

Fig 1. Immunocytochemical localization of NPR-B in renal cortex (A,D) and papillae (B,C). Sections labeled with anti-NPR-B in the absence (A,B) or presence (C,D) of the corresponding antigen. Long arrows, positive glomerular tuft staining. Arrow heads, positive arteriole staining. Short arrows, positive papillary capillary staining.

Venuto, 1988; de Leon & Garcia, 1992). Most of glomerular receptors are localized in mesangial cells (Bianchi *et al*, 1986). Pharmacological, physiological and biochemical evidence has suggested the existence of a heterogeneity in the ANG II receptor population which has been classified recently with nonpeptide ANG II antagonists (Chiu *et al*, 1990).

The AT_1 receptor subtype is selectively blocked by compounds typified by losartan, whereas the AT_2 receptor subtype is blocked by compounds such as PD123319. Both receptors have been cloned and shown to

possess 7 transmembrane domains (Murphy *et al*, 1991; Nukoyama *et al*, 1993). The AT_1 receptor subtype is positively coupled to phospholipase C (PLC) and negatively coupled to adenylate cyclase and seems to mediate all known physiological effects of ANG II. Upon AT_1 receptor binding, G-protein activation results in PLC activation and hydrolysis of membrane bound phosphatidyl-inositol 4,5-bisphosphate into two intracellular messengers, inositol 1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG). The soluble IP_3 diffuses through the cytosol binding IP_3 receptors on the sarcoplasmic reticulum and opening Ca^{2+} channels providing a rapid increase in cytosolic Ca^{2+} initiating the contractile response of smooth muscle cells. In contrast to AT_1, the physiological effects of AT_2 are still unknown. Its coupling mechanism has not yet been clearly identified, though there are some evidence suggesting a linkage to a protein tyrosine phosphatase (Kambayashi *et al*, 1993), and it may play a role in development (Bernstein & Alexander, 1992).

We have recently reported that in rat renal glomeruli and preglomerular vessels ANG II receptors correspond to the AT_1 subtype. No AT_2 receptors were detected (de Leon, Garcia, 1992; Gauquelin, Garcia, 1992) (Fig 2). In rodents, there are two AT_1

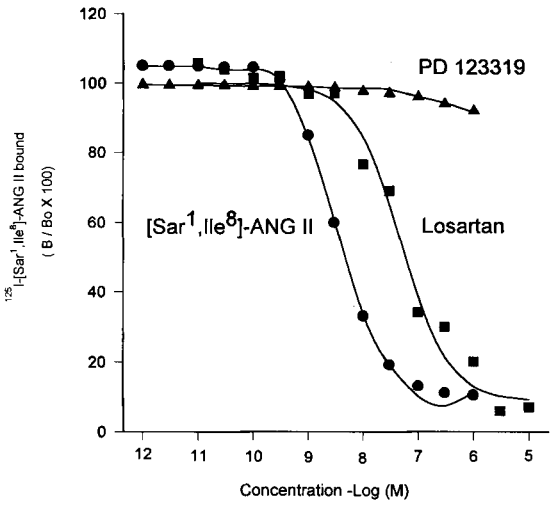

Fig 2. Representative competition binding curves of preglomerular vessels when non specific ANF II receptor antagonist [Sar^1, Ile^8]-ANG II (circles), AT_1 receptor antagonist losartan (squares) and AT_2 receptor antagonist PD123319 (triangles) were used. B and Bo represent binding in the respective presence and absence of the competitor.

isoforms, namely AT_{1A} and AT_{1B}, both coupled to G-proteins and both activate PLC, but whether they accomplish different functions has not yet been established. They have a 94% sequence identity (Bernstein & Alexander, 1992) and they cannot be pharmacologically differentiated (Chiu *et al*, 1993; Martin *et al*, 1995). The expression of both AT_{1A} and AT_{1B} subtypes is tissue-specific and each of them may play a specific, but still unknown, different role for ANG II action. In the rat kidney, the AT_1 mRNA was predominant in mesangial and juxtaglomerular cells, proximal tubules, vasa recta and interstitial cells, whereas the AT_{1B} isoform mRNA was detected in mesangial and juxtaglomerular cells and in the renal pelvis (Gase *et al*, 1994). It is, however, very surprising that no signal was detected in preglomerular vessels where a known effect of ANG II and specific receptor protein have been well documented (Brown & Venuto, 1988; de Leon & Garcia, 1992). The AT_{1A} subtype is also the main form (65%) in other rat vascular tissues such as the aorta (Llorens-Cortes *et al*, 1994). Decreases in plasma ANG II levels upregulate peripheral vascular and glomerular ANG II receptor, while high circulating levels induced the reverse effect (Aguilera & Catt, 1981; Beaufils *et al*, 1976; Bellucci & Wilkes, 1984). Contrariwise, ANG II receptor density in rat adrenal cortex parallel plasma ANG II levels (Douglas & Catt, 1976). Since in the rat kidney and adrenal cortex the predominant –if not exclusive form– is the AT_1 receptor subtype, those findings suggest that AT_{1A} and AT_{1B} may regulate in a differential way (Iwai *et al*, 1992; Du *et al*, 1995). Thus, in rat kidneys, ANG II infusion and high-salt diet down-regulate AT_{1B} in RNA, whereas ANG II infusion but not high-salt diet down-regulates AT_{1A} mRNA. On the other hand, the same authors (Du *et al*, 1995; Wang & Du, 1995; Wang *et al*, 1996) have reported that a low-sodium diet up-regulates AT_{1A} and down-regulates AT_{1B} mRNAs. The results are a bit contradictory and unfortunately, the experiments were performed in whole kidney homogenates which leaves unresolved in

which renal structure receptor regulation is taking place.

A simple method to purify renal preglomerular vessels (de Leon & Garcia, 1992) has allowed us to study separately the regulation of the AT_1 receptor protein in purified glomeruli and preglomerular microvessels. Thus, we (Amiri & Garcia, 1996) have reported that a 7-day low sodium diet down-regulates renal vascular but not glomerular AT_1 receptors. Furthermore, in a time-course study on the renin-dependent model of renovascular hypertension, the two-kidney, one clip, glomerular and vascular AT_1 receptor behaved in a divergent way (Amiri & Garcia, 1997). The same dissimilar behavior was observed in the spontaneously hypertensive rat, where only the renal vascular AT_1 receptor was upregulated and it was further upregulated by ACE inhibition without modifying that in glomeruli (Haddad & Garcia, 1996, 1997). Whether this dissimilar behavior is due to a different ratio of AT_{1A}/AT_{1B} in preglomerular vessels and mesangial cells is not known. No data are yet available on AT_1 receptor isoform protein in renal microvessels. We could not be surprised, however, if the ratio is different from that in glomeruli, since as demonstrated in our laboratory the density of ANF receptor or the type of ANF receptor in renal microvessels differ from other vascular beds (de Leon & Garcia, 1992; de Leon *et al*, 1995; Mendelsohn *et al*, 1987; Davis & Briggs, 1989).

ENDOTHELIN

Endothelin (ET), a potent vascular endothelium-derived vasoconstrictor, has been recently described (Hickey *et al*, 1985) and purified (Yanagisawa *et al*, 1988). Eventually, the gene encoding the peptide was cloned and its aminoacid sequence deduced (Sudoh *et al*, 1988). Endothelin consists of 21 aminoacids containing two interchain disulfide bonds and it is parent to a family of three peptides with high homology: ET-1, ET-2 and ET-3 (Doherty, 1992). The ET-1 gene is constitutively expressed in cultured endothelial cells as well as in some epithelial cell lines and has been found in every organ (Parker-Botelho *et al*, 1992). Plasma ET levels are relatively low (0.5 to 10 fmol/mL), but it has been reported that a 2-fold change in plasma ET levels, such as observed in chronic heart failure, may affect renal function without systemic effect (Clavell *et al*, 1995).

Two distinct ET receptors have been cloned: ET_A and ET_B. The ET_A receptor is mainly found in smooth muscle and cardiac cells and the ET_B receptor in vascular endothelium, but also in vascular smooth muscle cells and brain (Sokolovsky, 1991; Miyazaki *et al*, 1992). The two receptors share about 60% aminoacid identity. It has been suggested that there are at least two ET_B isoforms with different affinities to members of the ET/sarafotoxin family. Two distinct subclasses of ET_A receptors have been also detected in rat pituitary cells (Kanyicska & Freeman, 1993).

Intracellular Ca^{2+} modification and ET induced-PLC activation suggest that ET receptors are in close association with Ca^{2+} channels and PLC through G-proteins. Similarly to ANG II, ET activation of PLC results in phosphoinositide breakdown and protein kinase C (PKC) activation through DAG. Endothelin has been also shown to activate Na^+-H^+ exchanger, to enhance protein tyrosine phosphorylation and to stimulate phospholipase A (Resink *et al*, 1989). The ET_A receptor has higher affinity for ET-1. The ET_B receptor has an equal affinity for ET-1, ET-2, ET-3 and sarafotoxin S6c (Cox *et al*, 1984). Identification of ET binding sites has been facilitated by specific agonists and antagonists. BQ-123 is a very specific ET_A antagonist devoid of any agonist activity (Yano, 1992; Thibault *et al*, 1995). Recently, the BQ-788 compound, a high affinity, high specific AT_B antagonist devoid of any agonist activity, has been made available (Ishikawa *et al*, 1994).

Intravenous ET administration induces a strong and sustained pressor response (Yanagisawa *et al*, 1988) resulting from potent vasoconstriction, which is particularly important in renal, mesenteric

and pulmonary vascular beds (Miller *et al*, 1989; Lippton *et al*, 1988; Badr *et al*, 1989). Endothelin exerts several biological effects in the kidney, including vasoconstriction, with a reduction in renal blood flow and glomerular filtration rate, mesangial cell contraction and inhibition of Na^+,K^+-ATPase activity in papillary collecting tubes (Badr *et al*, 1989; King *et al*, 1989). It may also induce diuresis and natriuresis (Garcia *et al*, 1990). However, renal microvessels seem to be a major renal ET target. Endothelin-1 directly constricts renal microvessels (Edwards *et al*, 1990). It has also been suggested that ET-1 may mediate the renal vasoconstrictor effect of cyclosporine (Lanese & Conger, 1993). The renal effects of ET-1 are mediated by specific membrane receptors, but contradictory results have been reported as to which ET receptor isoform mediates ET-induced renal vasoconstriction (Cristol *et al*, 1993; Roubert *et al*, 1994). *In vitro*, preglomerular vascular vasoconstriction is totally inhibited by BQ123 (Lanese & Conger, 1993), suggesting a predominance of ET_A receptors.

Both ET_A and ET_B receptors are expressed in similar proportions in rat whole kidney homogenates (Roubert *et al*, 1994). However, when rat nephron segments are microdissected and ET receptor assessed by radioligand binding assays, a predominance of ET_B subtype has been reported in glomeruli and cortical collecting ducts (Takemoto *et al*, 1993). Ours (de Leon & Garcia, 1995) was the first report directly characterizing ET receptor subtypes in isolated rat renal preglomerular vessels. Thus, using a variety of ET_A and ET_B receptor agonists and antagonists we were able to establish that both receptors were expressed in almost equal proportion (de Leon & Garcia, 1995). Using specific ET_A and ET_B antagonists, BQ-123 and BQ-788 respectively, we have recently demonstrated (unpublished results, Fig 3) that whereas in preglomerular vessels both receptors are expressed in almost equal proportion, ET_B is expressed almost exclusively in glomeruli. Whether both receptors are regulated by locally generated or humoral ET levels has yet to be determined.

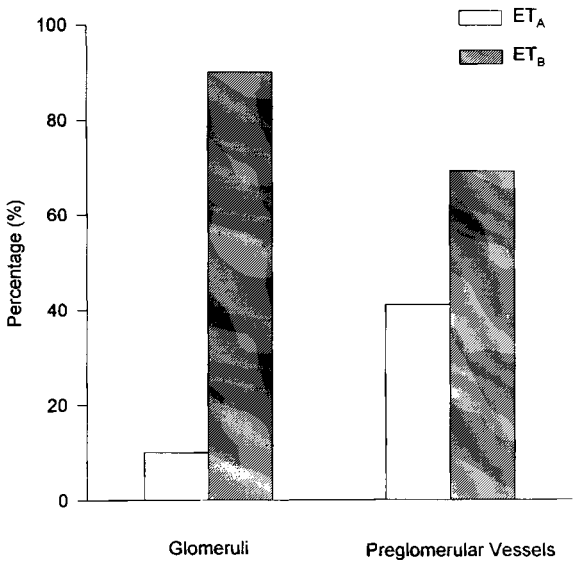

Fig 3. Relative proportion of ET_A and ET_B receptor subtypes in renal glomeruli and preglomerular vessels in the rat.

CONCLUSION

Specific high affinity ANF, ANG II and ET receptors are expressed in a variety of renal structures, where they play an important role in sodium and water homeostasis.

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