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Renal functional effects of endothelins: Dependency on cytochrome P450-derived arachidonate metabolites

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The renal tubular and hemodynamic effects of endothelin-1 (ET-1) were studied in the rat in terms of the participation of cytochrome P450 monooxygenases (CYP450)-derived arachidonic acid (AA) metabolites. The availability of specific mechanism-based inhibitors of CYP450-dependent AA metabolism has greatly facilitated studies designed to link AA metabolites generated by CYP450 to renal function. Eicosanoid products synthesized by cyclooxygenase (COX) and CYP450 can account for the renal functional effects of ET-1. Inhibition of COX decreased glomerular filtration rate (GFR) and potentiated the depression of GFR elicited by ET-1. In contrast, inhibition of CY-P450-dependent AA metabolism enhanced GFR and blunted ET-1 induced increase in renal vascular resistance, yet reduced the diuretic response to ET-1. Thus, CYP450-dependent AA products depress GFR and renal blood flow, while promoting sodium excretion. The effects of ET-1 on renal function correspond to those of 20-HETE, the predominant renal CYP450-derived AA metabolite.

Key terms: *cytochrome P450 arachidonate metabolites, eicosanoids, endothelin, hypertension, renal function, 20-hydroxy-eicosatetraenoic acid (20-HETE)*

INTRODUCTION

Arachidonic acid (AA) is metabolized through three pathways to generate distinct classes of eicosanoids with widely different biological actions: cyclooxygenase (COX) generates prostaglandins; lipoxygenases generate leukotrienes; and cytochrome P450 monooxygenases (CYP450). AA metabolism via CYP450 occurs by: 1) epoxidation, forming epoxy-eicosatrienoic acids (EETs); 2) subterminal hydroxylation forming regioisomeric cis-trans conjugated mono hydroxy-eicosatetraenoic acids, such as 16-, 17-, and 18-hydroxy-eicosatetraenoic acids (HETEs); and 3) ω/ω-1 hydroxylation, generating 19- and 20-HETEs. A role in cardiovascular and renal function was suggested for CYP450-AA products on the basis of their sites of synthesis in the heart, kidney and vasculature, and their properties which include effects on vasomotion and modulation of ion transport and cell growth (McGiff, 1991).

Of the CYP450-AA metabolites, 20-HETE stands out as a principal metabolite involved in the regulation of salt and water excretion and renal hemodynamics. 20-HETE is produced in the proximal tubules and the thick ascending limb (TAL) of Henle's loop of the rat, rabbit, and human kidney (Carroll *et al*, 1991; Omata *et al*, 1992), and in renal microvessels (Imig *et al*, 1996). 20-HETE is natriuretic when

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Biol Res 31: 209-215 (1998)

administered to anesthetized euvolemic rats (Takahashi *et al*, 1990); it retards ^{86}Rb uptake in medullary TAL cells isolated from the rabbit kidney by inhibiting the furosemide-sensitive Na^+-K^+-$2Cl^-$ cotransporter (Escalante *et al*, 1994).

In isolated blood vessels, 20-HETE elicits an endothelium- and COX-dependent vasoconstriction that is ascribed to its endoperoxide product, 20-OH-PGH_2 (Escalante *et al*, 1989; Schwartzman *et al*, 1989). 20-HETE has also been reported to constrict rat renal and cerebral microvessels (Harder *et al*, 1995; Imig *et al*, 1994). Inhibition of 20-HETE production attenuated the vasoconstrictor response of afferent arterioles to elevations in renal perfusion pressure and impaired autoregulation of renal blood flow (RBF) (Imig *et al*, 1994), thus implicating 20-HETE in the regulation of glomerular filtration rate (GFR) (Zou *et al*, 1994). A major role was suggested for 20-HETE in elevating blood pressure in the spontaneously hypertensive rat (SHR) (Sacerdoti *et al*, 1989; Omata *et al*, 1992). On the other hand, in the Dahl salt-sensitive rat, a deficiency in the production of this metabolite contributes to the elevation in TAL chloride transport and the development of hypertension (Roman *et al*, 1993).

CYP450-AA metabolites are stored in phospholipids and neutral lipids from which sites they can be released in response to hormonal stimulation of lipases (Carroll *et al*, 1997). Angiotensin 11 has been shown to release 20-HETE from the kidney despite inhibition of ω hydroxylase, signifying that these preformed metabolites are subject to hormonal release. Epoxide metabolites of CYP450 are major components in the vasodilator actions of hormones such as bradykinin and epidermal growth factor (Quilley *et al*, 1997). These studies provide the rationale for proposing CY-P450-AA metabolites as mediators/modulators of the renal hemodynamic and tubular responses to peptide hormones. We have established a close relationship between endothelins and 20-HETE, the eicosanoid acting as a second messenger for the peptide.

ENDOTHELINS

Endothelins (ETs) are 21-amino acid peptides which are encoded by three distinct genes: ET-1, -2, and -3. They are secreted at several sites where they act in both paracrine and autocrine mechanisms via ET receptors on target cells. Two distinct types of ET receptors, termed ET_A and ET_B have been identified, cloned, and sequenced (Sakurai *et al*, 1992) with limited evidence for a third receptor (ET_C) with uncertain physiological or pathophysiological effects. Activation of the ET_A receptor is associated with pronounced vasoconstriction whereas ET_B receptor occupation is linked to vasodilation (via ET_{B1}) and constriction (via ET_{B2}). In the rat kidney, ET_A receptors have been identified in vascular structures including glomeruli as well as in medullary collecting duct cells (Karet *et al*, 1993). Vascular smooth muscle expresses the ET_A and ET_{B1} receptor subtypes (Pollock *et al*, 1995).

Administration of ET-1 to the kidney leads to complex physiological alterations involving increased perfusion pressure, vasoconstriction, reduced glomerular filtration, and direct effects on tubular absorption as well as indirect effects related to the release of hormones affecting tubular function (Oyekan & McGiff, 1998). ET is produced in the kidney; immunoreactive ET (irET) has been identified in both vascular and tubular structures (Kohan, 1991; Kasinath *et al*, 1992). The renal papilla contains significant amounts of irET in both vasa recta and collecting duct cells. The most obvious renal effect of exogenous ET-1, and the first to be described, is its potent vasoconstrictor action leading to decreased RBF and GFR accompanied by an increase in renal perfusion pressure (Kon & Badr, 1991). On account of its ability to contract arteriolar smooth muscle and glomerular mesangial cells, a local modulatory role has been proposed for ET in the regulation of renal hemodynamic and secondarily excretory function. In the rat, ET-1 increased glomerular afferent and efferent arteriolar resistance and decreased the ultrafiltration coefficient (Badr *et al*, 1989; King *et al*, 1989), indicating a potential

role for this peptide in the control of renal vascular tone, GFR and mesangial cell function. ET-1 has been reported to elicit natriuresis/diuresis (King *et al*, 1989; Perico *et al*, 1990, 1991), despite reducing GFR and RBF. These effects have been variously attributed to increases in atrial natriuretic peptide (ANP) (Katoh *et al*, 1990; Perico *et al*, 1990), inhibition of arginine vasopressin (AVP)-stimulated cAMP in the collecting ducts (Miller *et al*, 1989) and inhibition of renal tubular Na^+-K^+-ATPase (Perico *et al*, 1991). ETs also possess cardiac inotropic and chronotropic effects (Ishikawa *et al*, 1988) which may secondarily affect renal function.

Endothelins stimulate phospholipases (Simonson & Dunn, 1991), resulting in release of free AA from membrane phospholipid stores and implicating oxygenase products of AA in some of its effects. COX products of AA metabolism mediate the bronchoconstrictor activity of ET in guinea pigs (Payne & Whittle, 1988); lipoxygenase products have been suggested to contribute to ET-1-induced diuresis and natriuresis in the rat (Perico *et al*, 1991). However, the contribution of CYP450-derived eicosanoids to the effects of ET-1 is unknown although there is indirect evidence that indicates a link between ETs and the CYP450 system. For example, major perturbations of renal function such as those caused by renal ischemia, are accompanied by enhanced CYP450-dependent AA metabolism (Carroll *et al*, 1988), as well as by increased ET-1 mRNA expression and renal vascular ET-1 binding affinity and receptor number (Firth & Ratcliffe, 1992; Kon & Awazu, 1992).

20-HETE MEDIATES THE RENAL FUNCTIONAL RESPONSE TO ET-1

ET-1-induced renal functional changes have been linked to production of CYP450-AA metabolites, especially 20-HETE in the isolated rat kidney, in the anesthetized rat and in the unanesthetized hypertensive rat treated with deoxycorticosterone acetate (DOCA) and salt. The availability of specific inhibitors of CYP450-AA metabolism has greatly facilitated studies designed to relate AA metabolites generated by CYP450 to biological effects of vasoactive agents. We have used selective inhibitors of 20-HETE production in the Kreb's-perfused isolated kidney and the blood-perfused *in situ* kidney to examine the contribution of the CY-P450 enzyme system to the vascular/hemodynamic and tubular actions of ET-1. The Kreb's-perfused kidney is highly sensitive to eicosanoids and allows addressing the vascular actions of vasoactive hormones in terms of a putative eicosanoid second messenger. This experimental preparation has a vascular sensitivity to ET-1 and eicosanoids that is comparable to that of the blood-perfused kidney (Oyekan *et al*, 1997; Malik & McGiff, 1975). The effects of inhibition of CYP450 monooxygenase activity on the renal vasoconstrictor activity of ET-1 and renal efflux of 20-HETE were evaluated. ET-1 at 0.3, 1.0 and 3.0 pmol/kg/min, given intravenously, elicited renal vasoconstriction in a dose-dependent manner, increasing renal vascular resistance (RVR) by about 150% at the highest dose (Fig 1) In kidneys treated with ETYA (10 μM), the all-purpose inhibitor of the three pathways of AA metabolism, ET-1-induced increases in RVR were reduced by ~70% ($p < 0.05$), whereas the vasoconstrictor responses to U-46619, the PGH_2/TxA_2-mimetic (negative control), were not affected, indicating that ETYA did not alter eicosanoid receptor responsiveness. ET-1 (1 pmol) elicited a four-fold increase in the release of 20-HETE into the renal effluent associated with renal vasoconstriction. Dibromododec-11-enoic acid (DBDD; 2 μM), a specific mechanism-based inhibitor of ω/ω-1 hydroxylase, blunted the renal vasoconstrictor responses to ET-1, reducing the increases in RVR by ~40% (Fig 1) associated with a significant reduction in the release of 20-HETE from the kidney (Fig 2). These findings provided the rationale for studying possible participation of CYP450 arachidonate metabolites in the renal excretory response to ET-1. 20-HETE produced natriuresis in rats (Takahashi *et al*, 1990) despite increasing RVR (Imig *et al*, 1996) and

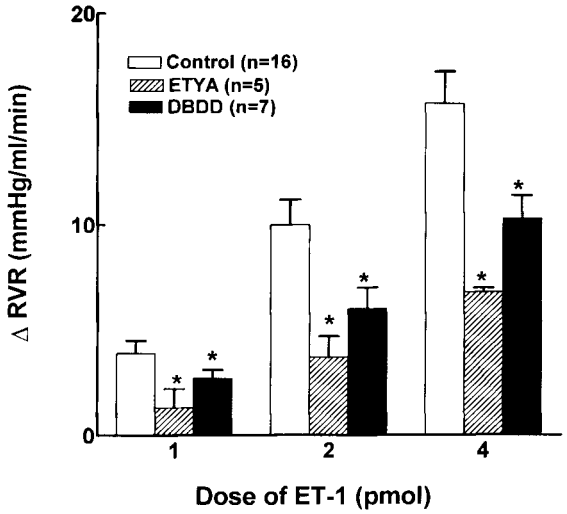

Fig 1. Effects of ETYA (10 μM) and DBDD (2 μM) on dose-dependent increase in renal vascular resistance (RVR) elicited by ET-1 (1, 2 and 4 pmol) given by bolus injection into the perfusate line in Krebs-perfused rat isolated kidney. Control kidneys were treated with 95% ethanol (the vehicle for ETYA and DBDD). * $p < 0.05$ *vs* Control.

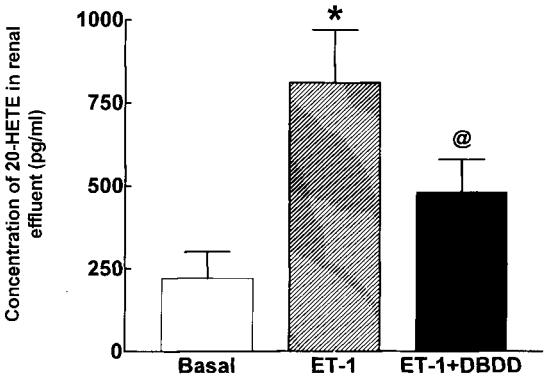

Fig 2. 20-HETE released into the renal effluents of Krebs-perfused isolated indomethacin-treated (2.8 μM) rat kidneys following challenge with bolus injections of ET-1 (1 pmol). Effluents collected before (Basal) and after administration of ET-1 alone (ET-1) or ET-1 in the presence of DBDD (ET-1 + DBDD) were subjected to gas chromatography/mass spectrometric analysis for 20-HETE. * $p < 0.05$ *vs* Basal. @ $p < 0.05$ *vs* ET-1.

depressing GFR, responses which resemble the actions of ET-1 on renal function. As the role of CYP450-AA metabolites in the renal excretory response to ET-1 had not been addressed *in vivo,* we hypothesized that 20-HETE is an essential component of the renal tubular and hemodynamic effects of ET-1. In the blood-perfused rat kidney, infusion of ET-1 (0.3, 1 and 3 pmol/kg/min) resulted in dose-dependent increases in Na^+ excretion ($U_{Na}V$) (Fig 3) despite negative hemodynamic effects. The highest dose of ET-1 (3 pmol/kg/min) reduced GFR by 32 ± 4% indicating that ET-1 evoked direct tubular effects to promote natriuresis. DBDD attenuated ET-1-induced increases in $U_{Na}V$ by 37 ± 4% (Fig 4a) despite reversal of the ET-1-induced reductions in GFR (Fig 4b). The excretory effects of ET-1, therefore, were mediated by a CYP450 product, probably 20-HETE, as the diuretic-natriuretic action of ET-1 was attenuated by DBDD, an inhibitor of the ω/ω-1 hydroxylase pathway of AA metabolism.

ET-1, 20-RETE AND RENAL INJURY

The pathophysiological relevance of the interactions between ET-1 and 20-HETE was evaluated using the DOCA/salt uninephrectomized (UNx) hypertensive rat. There were a number of reasons for studying this hypertensive model. First, there is a distinctive and well documented overexpression of ET-1 with regard to content of irET-1 and abundance of ET-1 mRNA in the blood vessels of DOCA/salt hypertensive rats (Lariviere *et al*, 1993a, b). Second, changes in the activity of renal

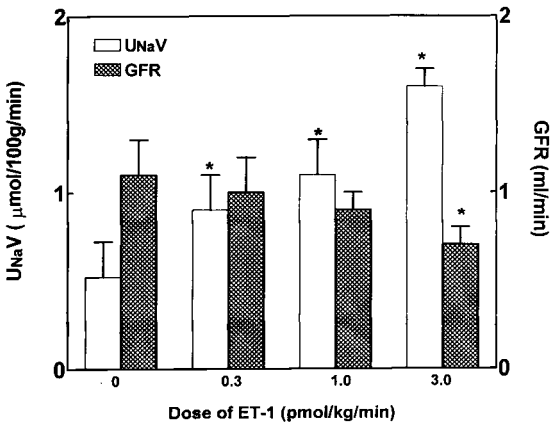

Fig 3. Effects of ET-1 (0.3, 1.0, and 3.0 pmol/kg/min i.v.) on urinary Na^+ excretion ($U_{Na}V$) and GFR in inactin (100 mg/kg ip)-anesthetized euvolemic rats. Data presented as means ± SE. They represent $U_{Na}V$ over 30-min collection periods during infusion of 0.9% NaCl (ET 0) or ET-1 (pmol/kg/min). * $p < 0.05$ *vs* ET-1 (0).

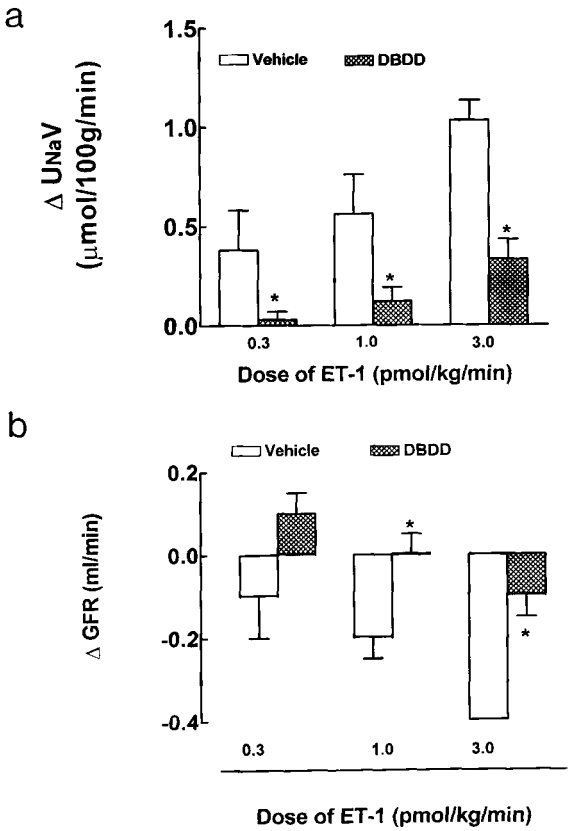

Fig 4. Effects of ET-1 (0.3, 1.0, and 3.0 pmol/kg/min i.v.) on changes in $U_{Na}V$ (**a**) and GFR (**b**) in the presence of DBDD (12.5 μg/min renal intra-arterial infusion; DBDD group; n = 5) or 50% ethanol (Vehicle). Doses of ET-1 are shown in parentheses. Data presented as means ± SE. * $p < 0.05$ *vs* Vehicle.

CYP450 activity during sodium loading (Capdevilla *et al*, 1992; Makita *et al*, 1994), uninephrectomy (Takahashi *et al*, 1993) and following treatment with DOCA (Lapuerta *et al*, 1988) suggest that CYP450-AA products participate in volume-dependent hypertension. The UNx/salt/DOCA rat should provide a unique model to establish a link between ET-1 and 20-HETE. Hypertension was induced by implanting DOCA pellets and providing 1% NaCl in the drinking water to UNx rats treated with $CoCl_2$ to deplete CYP450 enzymes. $CoCl_2$ induces heme oxygenase, leading to accelerated degradation of heme including that associated with CYP450, thereby depleting CYP450 enzymes and interfering with their ability to metabolize AA (Da Silva *et al*, 1994). In UNx/salt/DOCA rats, systolic blood pressure rose steadily from 103 ± 7 on day 3 to 193 ± 6 mm Hg on day 21 (Fig 5), a pressor response prevented by $CoCl_2$ treatment. Concomitant with these changes, urinary excretion of irET-1 and 20-HETE increased four-fold between day 3 and day 21 from control levels in UNx/salt/DOCA (Figs 6a, 6b); treatment with $CoCl_2$ (UNx/salt/DOCA + $CoCl_2$) prevented the increased excretion of ET-1 and 20-HETE.

As urinary excretion of 20-HETE and ET-1 increased in association with elevation of blood pressure and proteinuria, we suggest an essential role for 20-HETE in the pathophysiological changes produced in DOCA/salt hypertension. Increased 20-HETE excretion occurring in parallel with ET-1 excretion suggests that endogenous production of 20-HETE is related to ET-1 production and favors our proposed role for 20-HETE as the second messenger in the renal functional effects of ET-1. These findings support the linkage of eicosanoid products generated by CYP450 to the renal functional effects of ET-1. An extension of this peptide-eicosanoid interaction to the renal tubular effects of ET-1 revealed that administration of DBDD abolished the ability of ET-1 to promote natriuresis

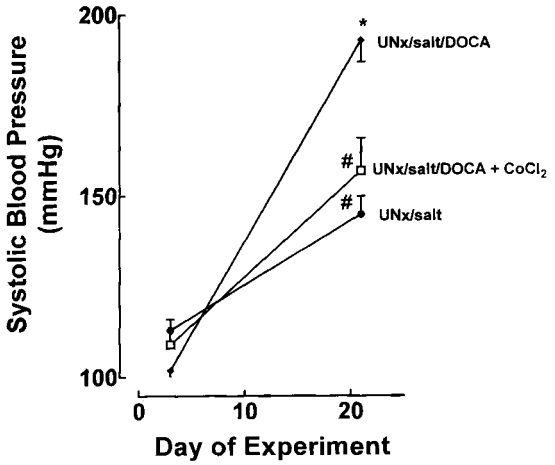

Fig 5. Systolic blood pressure (as determined by tail plethysmography) on days 3 and 21 in salt (1% NaCl)-drinking uninephrectomized (UNx/salt; n = 5) controls, salt-drinking uninephrectomized rats that received DOCA (25 mg) pellet and treated with vehicle (0.9% NaCl, 1 ml/kg ip) (UNx/salt/DOCA; n = 5) or $CoCl_2$ (24 mg/kg ip) (UNx/salt/DOCA + $CoCl_2$; n = 5). Data presented as means ± SE. * $p < 0.05$ vs UNx/salt. # $p < 0.05$ *vs* UNx/salt/DOCA

Biol Res 31: 209-215 (1998)

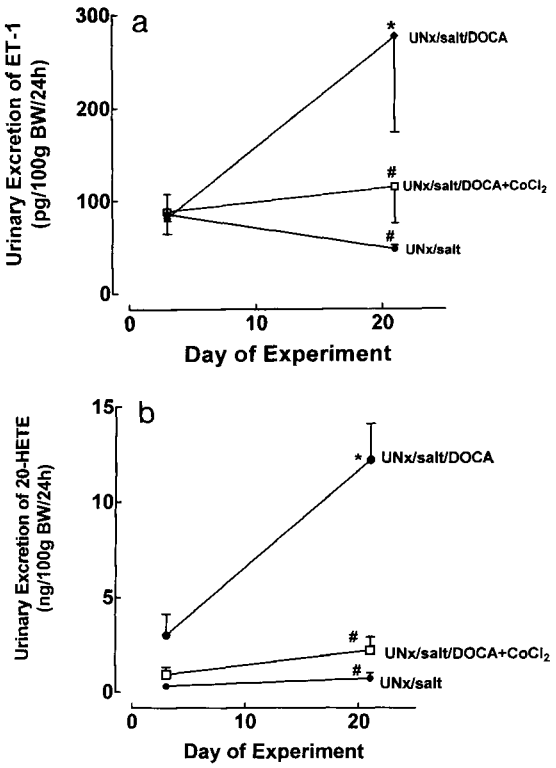

Fig 6. Urinary excretion of immunoreactive ET-1 (a) and 20-HETE (b) on days 3 and 21 in uninephrectomized control rats (UNx/salt; n = 5), vehicle-treated rats that received DOCA (UNx/salt/DOCA; n = 5) or $CoCl_2$-treated salt-drinking uninephrectomized DOCA/salt-treated rats (UNx/salt/DOCA + $CoCl_2$; n = 5). ET-1 was determined by radioimmunoassay and 20-HETE by GC/MS. Data presented as means ± SE. * $p < 0.05$ *vs* UNx/salt. # $p < 0.05$ *vs* UNx/salt/DOCA.

despite reversal of the negative effects of ET-1 on GFR. A pathophysiological role was suggested for 20-HETE as a potential mediator of endothelin-induced functional changes in DOCA/salt hypertension since 20-HETE and ET-1 increased in parallel in rats that developed hypertension in response to DOCA/salt treatment. As depletion of CYP450 enzymes with $CoCl_2$ prevented the renal pathophysiological response to DOCA/salt treatment, renal production of CYP450-AA metabolites was considered to be linked to increased ET-1 levels in the kidney.

In conclusion, 20-HETE is involved in regulating vasomotion at crucial sites such as preglomerular microvessels, as well as ion transport in proximal tubules and TAL. Studies directed towards integrating the activities of vasoactive peptides, nitric oxide (NO), and cytokines with those of CYP450-derived arachidonate metabolites hold great promise for the development of novel therapeutic strategies for treating hypertension, diabetes, heart failure and the complications resulting from primary diseases of the kidney and liver.

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