

Attenuated renal response to moxonidine and rilmenidine in one kidney-one clip hypertensive rats

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1 I₁ non-adrenoceptor, imidazoline receptor agonists, such as moxonidine, increase urine flow rate and sodium excretion following infusion into the renal artery. The functions of these agonists in genetic and acquired models of hypertension have not been determined.

2 We therefore studied the renal effects of two known non-adrenoceptor, imidazoline receptor agonists, rilmenidine and moxonidine, in 1K-1C hypertensive and 1K-sham normotensive rats. Rilmenidine (0, 3, 10, 30 nmol kg⁻¹ min⁻¹) or moxonidine (0, 1, 3, 10 nmol kg⁻¹ min⁻¹) was infused directly into the renal artery (30 gauge needle) of 1K-sham normotensive and 1K-1C hypertensive rats.

3 In 1K-sham normotensive rats, rilmenidine and moxonidine produced dose related increases in urine flow rate, sodium excretion and osmolar clearance. Both rilmenidine and moxonidine failed to increase urine flow rate, sodium excretion and osmolar clearance in 1K-1C hypertensive rats to the same extent as in 1K-sham animals. At comparable doses, rilmenidine had no effect, while moxonidine (3 and 10 nmol kg⁻¹ min⁻¹) did result in a small increase in urine volume and osmolar clearance which was less than that observed in the 1K sham control animals.

4 These studies indicate that the renal effects of non-adrenoceptor, imidazoline receptor stimulation are diminished in 1K-1C hypertensive rats compared with 1K-sham normotensive rats. Whether this decrease in activity of the natriuretic non-adrenoceptor, imidazoline receptors contributes to the increase in blood pressure in the 1K-1C acquired model of hypertension remains to be determined.

Keywords: Rilmenidine; moxonidine; one kidney-one clip hypertension; non-adrenoceptor, imidazoline receptors

Introduction

In acquired forms of hypertension, renal α -adrenoceptor density has been found to be unchanged or decreased (Yamada *et al.*, 1980; Fukuda *et al.*, 1983; Saiz *et al.*, 1987; Michel *et al.*, 1989b; Wilson, 1991), whereas in spontaneously hypertensive rats, the density of renal α_2 -adrenoceptors has been found to be elevated as compared to Wistar-Kyoto rats (Pettinger *et al.*, 1982; Saiz *et al.*, 1987; Sanchez *et al.*, 1989; Michel *et al.*, 1990a). Furthermore, previous studies in our laboratory indicated that the renal response to α_2 -adrenoceptor agonists such as clonidine was decreased in spontaneously hypertensive rats (Li *et al.*, 1992) but not in one kidney, one clip (1K-1C) hypertensive rats (Li & Smyth, 1994). The diuretic and natriuretic effects of α_2 -adrenoceptor stimulation have been shown to be mediated by an inhibition of the renal action of vasopressin (Blandford & Smyth, 1990; Gellai, 1990). Thus, the decreased renal response to a V₂-vasopressin receptor antagonist in spontaneously hypertensive rats but not 1K-1C hypertensive rats (Li & Smyth, 1993) was consistent with the decreased response to α_2 -adrenoceptor stimulation in this model of genetic hypertension.

Recent studies in our laboratory have proposed that the effects of two purported α_2 -adrenoceptor agonists, clonidine and 2,6-dimethyl clonidine (2,6-DMC), may in fact be mediated by two α_2 -adrenoceptor subtypes or two distinct receptors, α_2 -adrenoceptors and non-adrenoceptor, imidazoline receptors (Smyth *et al.*, 1992a). Whereas 2,6-DMC caused an increase in urine flow rate which was secondary to an increase in osmolar clearance, clonidine resulted in an increase in urine flow rate which was secondary to an increase in free water clearance (Smyth *et al.*, 1992a). Furthermore, we have recently found that the effects of 2,6-DMC but not clonidine were significantly attenuated in rats with 1K-1C hypertension (Li & Smyth, 1994) and there was a decrease in [³H]-idazoxan binding sites in kidneys from 1K-1C hypertensive rats. The

renal actions of 2,6-DMC can be antagonized by idazoxan (Smyth & Li, 1991) which would be consistent with those effects being mediated by the non-adrenoceptor, imidazoline receptor (Feldman *et al.*, 1990; Gomez *et al.*, 1991; Allan *et al.*, 1993). Nevertheless, it has not been determined as to whether the decreased response to 2,6-DMC was due to a decreased activity at the α_2 -adrenoceptor or the non-adrenoceptor, imidazoline receptor.

In the present study, we determined whether or not, in 1K-1C hypertensive rats, a decreased response was found with non-adrenoceptor, imidazoline receptor agonists in general. Two agonists (rilmenidine and moxonidine) which have been shown to display a much greater selectivity and affinity for the I₁ non-adrenoceptor, imidazoline receptor over the α_2 -adrenoceptor (Ernsberger *et al.*, 1992), were used to investigate further the non-adrenoceptor, imidazoline receptor in 1K-1C hypertensive and 1K-sham normotensive rats.

Methods

Experimental animals

The standard procedures have been described previously (Blandford & Smyth, 1988; 1990). Male Sprague-Dawley rats (100–125 g) were obtained from the University of Manitoba (Charles River Breeding Stock) and cared for according to regional animal care standards protocol. Animals were housed at 22°C with an environmental humidity maintained at 50% with a light/dark cycle from 07 h 00 min to 19 h 00 min. Rats were fed Purina rat chow and received tap water for drinking.

The animals were separated into two groups. In the first group (1K-1C), rats were anaesthetized with ether and the kidneys exposed by an abdominal incision. A silver clip

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(0.254 mm) was placed around the left renal artery and the right kidney was removed. In the second group (1K-sham), animals underwent the identical procedure except, when the left renal artery was separated from the renal vein, no silver clip was placed around the artery and the right kidney was removed. The animals were kept for 12 to 16 days after surgery and subsequently underwent the protocol described below.

Renal effects of rilmenidine or moxonidine

On the day of the experiment, the rats were anaesthetized with pentobarbitone (BDH Chemicals, Poole, England; 50 mg kg⁻¹, i.p.). Additional anaesthetic was administered in a bolus dose of 3 mg kg⁻¹ i.v. as needed. The rats were placed on a thermostatically controlled heating blanket. The rectal thermometer was connected to a Harvard Animal Blanket Control Unit which was used to maintain body temperature at 37.5°C. The trachea was cannulated with polyethylene tubing (PE-240) and the animal was allowed to breathe spontaneously. The left carotid artery was cannulated with polyethylene tubing (PE-50) and blood pressure was measured with a Statham pressure transducer (model P23Dc) connected to a Grass Polygraph Model V. The left jugular vein was cannulated (PE-160) and connected to an infusion pump (Syringe pump model 355) for the infusion of saline. The left kidney was exposed by a flank incision and the left ureter was cannulated (PE-50) for the collection of urine. A 30 gauge stainless steel needle was inserted into the aorta and advanced into the origin of the left renal artery. A single drop of glue (Superglue, LePage's Limited) was used to secure the base of the needle to surrounding tissue. This was connected by Tygon Tubing (size 0.25 mm) to an infusion pump (Harvard infusion/withdrawal pump model 600-900) for infusion of either saline or study drug at 3.4 µl min⁻¹.

Following the surgical procedure, saline was administered by intravenous infusion (97 µl min⁻¹). The animals were allowed to stabilize for a 45 min period. After the stabilization period, a 15 min control urine collection was obtained. This was followed by infusion of saline (vehicle), rilmenidine (3, 10 or 30 nmol kg⁻¹ min⁻¹) or moxonidine (1, 3 or 10 nmol kg⁻¹ min⁻¹) directly into the renal artery for the duration of the experiment at 3.4 µl min⁻¹. During this infusion, two additional urine collections of 15 min and 45 min were obtained into preweighed tubes.

The sodium concentration in plasma and urine were determined with a Beckman KLiNa Flame Photometer. Creatinine concentration was determined with a Beckman

Creatinine Analyzer Model 2. The urine and plasma osmolality was analysed with a MicroOsmette (Precision Systems). Urine volume was determined gravimetrically.

Data analysis

All data are presented as the mean ± the standard error of the mean (s.e.mean). Statistical analysis was performed with a repeated-measures ANOVA using SAS System Version 6.07. Significant interactions were further analyzed with Least Squares Means Difference Test. Baseline values (first urine collection) prior to the administration of the saline vehicle or study drugs (moxonidine and rilmenidine) were compared and presented in table format. The effects of the saline vehicle and study drugs were expressed graphically as the absolute change from the first to final urine collection period. This allowed the determination of the magnitude of the changes for each variable within the different groups. Each group comprised 5 to 8 animals. In the figures, *denotes $P < 0.05$ between groups (1K vs 1K-1C) receiving the same drug infusion rate and #denotes $P < 0.05$ as compared with the control within the same group receiving the vehicle infusion.

Drugs

Moxonidine (supplied by Beiersdorf, AG, Hamburg, Germany) and rilmenidine (supplied by I.R.I. Servier, France) were used.

Results

Effect of intrarenal infusion of rilmenidine

Baseline values for experimental groups prior to the administration of the experimental treatments (vehicle, rilmenidine) are shown in Table 1. The first collection period was used as an indication of the effects of the surgical preparation in the different groups. The baseline values were similar for all the different doses within either the 1K sham or 1K-1C hypertensive groups. The 1K-1C hypertensive rats consistently had higher blood pressures ($P < 0.05$) than the 1K sham animals. The incidence of hypertension in the animals which received the renal clip was 100%.

The mean arterial blood pressure was not altered by rilmenidine in either the 1K-sham normotensive rats or the 1K-1C hypertensive rats (Figure 1). Heart rate was decreased

Table 1 Absolute baseline values for experimental groups prior to the administration of vehicle (0 nmol kg⁻¹ min⁻¹) or rilmenidine (3, 10 and 30 nmol kg⁻¹ min⁻¹)

	1K-Sham				Rilmenidine			
	0	3	10	30	0	3	10	30
BP (mmHg)	121 ± 2	126 ± 1	130 ± 4	127 ± 3	175 ± 7 ^a	150 ± 10 ^a	165 ± 4 ^a	168 ± 7 ^a
HR (b.p.m.)	433 ± 10	423 ± 14	427 ± 6	420 ± 19	447 ± 8	417 ± 15	437 ± 13	463 ± 6
C _{cr} (ml min ⁻¹)	1.6 ± 0.3	1.8 ± 0.2	1.5 ± 0.1	1.5 ± 0.1	1.6 ± 0.2	2.0 ± 0.4	1.5 ± 0.2	1.5 ± 0.2
UV (µl min ⁻¹)	14 ± 2	19 ± 4	15 ± 2	17 ± 3	13 ± 1	14 ± 2	16 ± 2	20 ± 3
UNaV (µEq min ⁻¹)	2.0 ± 0.4	3.3 ± 0.6	2.9 ± 0.8	2.7 ± 0.6	1.8 ± 0.2	2.2 ± 0.8	2.0 ± 0.5	3.4 ± 0.7
C _{osm} (µl min ⁻¹)	53 ± 4	74 ± 9	64 ± 6	54 ± 6	46 ± 3	58 ± 8	57 ± 6	63 ± 8
C _{H₂O} (µl min ⁻¹)	-39 ± 4	-56 ± 5	-49 ± 5	-38 ± 4	-33 ± 3	-44 ± 7	-41 ± 6	-43 ± 5

BP, blood pressure; HR, heart rate; C_{cr}, creatinine clearance; UV, urine flow rate; UNaV, sodium excretion; C_{osm}, osmolar clearance; C_{H₂O}, free water clearance. Values represent mean ± standard error. ^a denotes $P < 0.05$ between 1K-sham normotensives and 1K-1C hypertensive rats.

only in 1K-1C rats at the highest infusion rate of rilmenidine ($30 \text{ nmol kg}^{-1} \text{ min}^{-1}$). Rilmenidine did not alter creatinine clearance. All doses of rilmenidine resulted in an increase in urine flow rate and sodium excretion in 1K-sham rats (Figure 2). However, in 1K-1C hypertensive rats, no change in urine flow rate or sodium excretion was observed (Figure 2). This was reflected in significantly greater sodium excretions and urine flow rates for all doses in the 1K-sham animals. Rilmenidine increased osmolar clearance in 1K-sham normotensive rats but failed to have any effect in 1K-1C hypertensive rats (Figure 3). Free water clearance was not significantly altered in 1K-sham rats or 1K-1C hypertensive rats (Figure 3).

Effect of intrarenal infusion of moxonidine

Baseline values for experimental groups prior to the administration of the experimental treatments (vehicle, moxonidine)

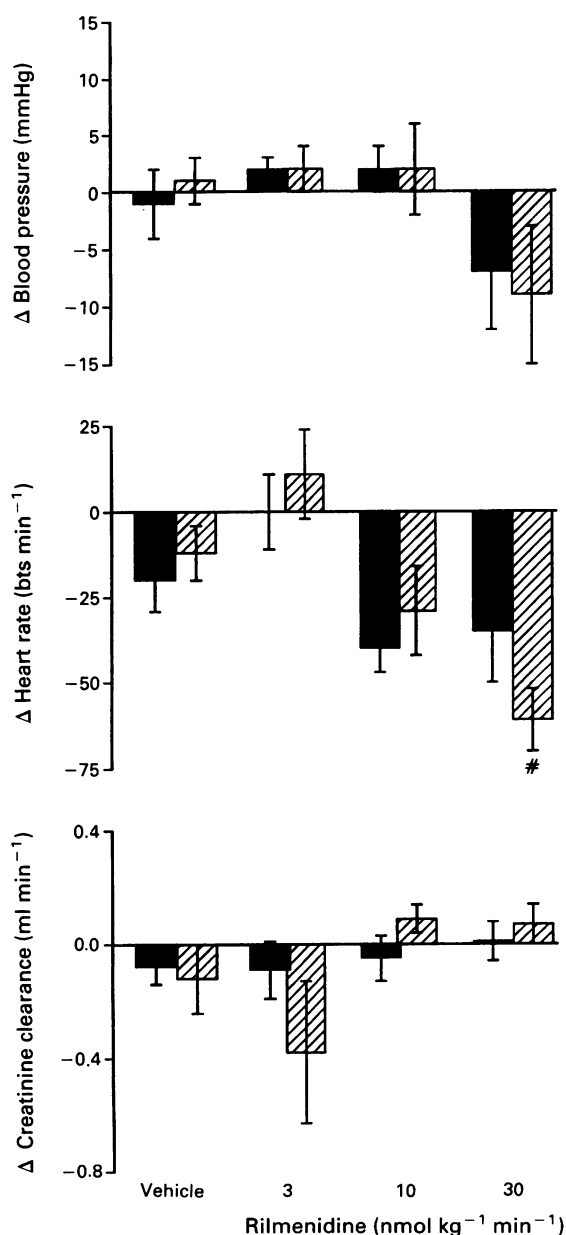


Figure 1 The effects of rilmenidine on mean arterial blood pressure, heart rate and creatinine clearance. Data are presented as means \pm standard error of the mean. The solid columns represent the 1K-sham rats and the hatched columns represent the 1K-1C hypertensive rats. #denotes $P < 0.05$ as compared with the respective control group.

are shown in Table 2. The first collection period was used as an indication of the effects of the surgical preparation in the different groups. As would be anticipated, a significant interaction effect by group (1K Sham versus 1K-1C) was observed for blood pressure in that the animals which had received renal clips had a significantly higher blood pressure ($P < 0.05$). Within the 1K sham rats the baseline values for heart rate (HR), osmolar clearance (C_{osm}) and free water clearance ($C_{\text{H}_2\text{O}}$) in the animals that received $3 \text{ nmol kg}^{-1} \text{ min}^{-1}$ of moxonidine were different from the group which received the saline vehicle (Table 2). The differences were, a lower heart rate, increased osmolar clearance and decreased free water clearance (Table 2).

The mean arterial blood pressure was not altered by moxonidine in either the 1K-sham normotensive rats or the 1K-1C hypertensive rats (Figure 4). Heart rate was decreased in both 1K-sham and 1K-1C rats at the highest infusion rate of moxonidine ($10 \text{ nmol kg}^{-1} \text{ min}^{-1}$). Moxonidine did not alter creatinine clearance. All doses of moxonidine resulted in an increase in urine flow rate in 1K-sham rats (Figure 5), whereas, in 1K-1C hypertensive rats, the two highest infusion rates increased urine flow rate (Figure 5). The increase in urine flow rate was also greater in the 1K-sham rats as compared to the 1K-1C rats. Sodium excretion was also increased by moxonidine in 1K-sham normotensive rats at all infusion rates investigated, but only at the highest infusion rate in 1K-1C hypertensive rats (Figure 5). Moxonidine increased osmolar clearance at all infusion rates investigated in 1K-sham normotensive rats but only at the highest dose in 1K-1C hypertensive rats (Figure 6). Free water clearance was increased in the 1K-sham rats at the lowest and highest doses of moxonidine but not the 1K-1C hypertensive rats.

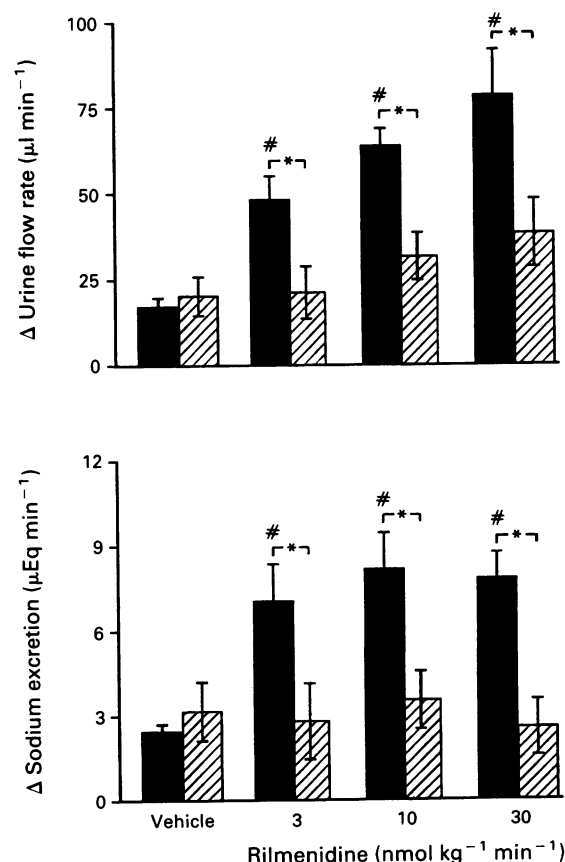


Figure 2 The effects of rilmenidine on urine flow rate and sodium excretion. The solid columns represent the 1K-sham rats and the hatched columns represent the 1K-1C hypertensive rats. #denotes $P < 0.05$ between 1K-sham normotensive and 1K-1C hypertensive rats. # $P < 0.05$ as compared with the respective control group.

Table 2 Absolute baseline values for experimental groups prior to the administration of vehicle ($0 \text{ nmol kg}^{-1} \text{ min}^{-1}$) or moxonidine (1, 3 and $10 \text{ nmol kg}^{-1} \text{ min}^{-1}$)

	1K-Sham				Moxonidine			
	0	1	3	10	0	1	3	10
BP (mmHg)	121 ± 2	121 ± 2	120 ± 1	132 ± 4	175 ± 7 ^a	157 ± 6 ^a	157 ± 3 ^a	161 ± 5 ^a
HR (b.p.m.)	433 ± 10	447 ± 11	393 ± 8 [*]	440 ± 11	447 ± 8	440 ± 9	427 ± 10	455 ± 11
C _{cr} (ml min ⁻¹)	1.6 ± 0.3	1.5 ± 0.1	2.1 ± 0.2	1.6 ± 0.1	1.6 ± 0.2	1.4 ± 0.1	1.7 ± 0.4	1.5 ± 0.1
UV (μl min ⁻¹)	14 ± 2	16 ± 1	17 ± 2	15 ± 3	13 ± 1	12 ± 2	16 ± 3	13 ± 1
UNaV (μEq min ⁻¹)	2.0 ± 0.4	3.5 ± 0.4	3.1 ± 0.6	2.9 ± 0.8	1.8 ± 0.2	2.1 ± 0.6	2.7 ± 0.3	1.9 ± 0.2
C _{osm} (μl min ⁻¹)	53 ± 4	65 ± 6	80 ± 6 [*]	60 ± 9	46 ± 3	48 ± 5	57 ± 3	50 ± 3
C _{H₂O} (μl min ⁻¹)	-39 ± 4	-50 ± 4	-63 ± 6 [*]	-45 ± 7	-33 ± 3	-36 ± 5	-41 ± 4	-37 ± 2

BP, blood pressure; HR, heart rate; C_{cr}, creatinine clearance; UV, urine flow rate; UNaV, sodium excretion; C_{osm}, osmolar clearance; C_{H₂O}, free water clearance. Values represent mean ± standard error. ^a denotes $P < 0.05$ between 1K-sham normotensives and 1K-1C hypertensive rats and ^{*}denotes $P < 0.05$ versus the vehicle control group (0) within the 1K-sham or 1K-1C groups.

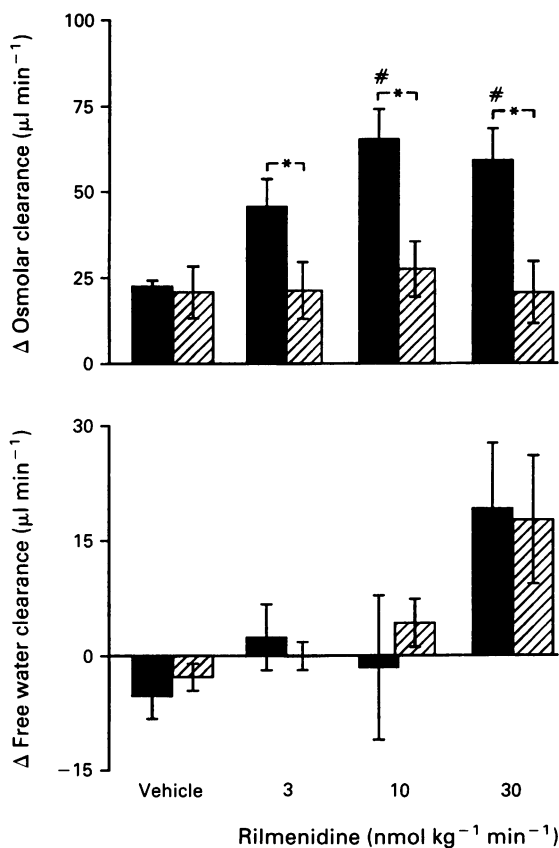


Figure 3 The effects of rilmenidine on free water clearance and osmolar clearance. The solid columns represent the 1K-sham rats and the hatched columns represent the 1K-1C hypertensive rats. ^{*}denotes $P < 0.05$ between 1K-sham normotensive and 1K-1C hypertensive rats. [#]denotes $P < 0.05$ as compared with the respective control group.

Discussion

Boyajian *et al.* (1987) and Coupry *et al.* (1987) reported that two purported α_2 -adrenoceptor antagonists, rauwolscine and idazoxan, labelled two distinct populations of receptors. Michel *et al.* (1989a; 1990b) also found that [³H]-idazoxan

labelled a non-adrenoceptor site which was distinct from the α_2 -adrenoceptor. These non-adrenoceptor sites also had a greater affinity for imidazoline based compounds than phenylethylamines (catecholamines) (Bricca *et al.*, 1989; Ernsberger *et al.*, 1990). Recently these non-adrenoceptor, imidazoline sites have been found to exist as at least two subtypes, the I₁ which was labelled by [³H]-clonidine and the I₂ which was labelled by [³H]-idazoxan (Ernsberger *et al.*, 1992; Reis *et al.*, 1992).

A number of lines of evidence suggested that 2,6-DMC may be a non-adrenoceptor, imidazoline receptor agonist. Previous studies in our laboratory indicated that the two purported α_2 -adrenoceptor agonists 2,6-DMC and clonidine increased urine flow rate by two distinct mechanisms (Smyth *et al.*, 1992a). 2,6-DMC increased urine flow rate secondary to an increase in osmolar clearance while clonidine increased urine flow rate by increasing free water clearance. In addition, pretreatment with a V₂ vasopressin antagonist had no effect on the response to 2,6-DMC but completely attenuated the effects of clonidine. These results are consistent with the effects of 2,6-DMC and clonidine being mediated by two distinct mechanisms and/or sites, α_2 -adrenoceptors and non-adrenoceptor, imidazoline receptors (Smyth *et al.*, 1992a). Effects similar to those reported with 2,6-DMC have been found by Allan *et al.* (1993) using moxonidine, an I₁ non-adrenoceptor, imidazoline receptor agonist with an approximately 700 times higher affinity for I₁ non-adrenoceptor, imidazoline receptors than that for α_2 -adrenoceptors in the kidney (Ernsberger *et al.*, 1993). They found that moxonidine produced an increased urine flow rate in Sprague-Dawley rats and this increase was secondary to an increase in osmolar clearance. This increase was blocked by pretreatment with idazoxan (non-adrenoceptor, imidazoline receptor antagonist) but not by pretreatment with rauwolscine (α_2 -adrenoceptor antagonist). The renal effects of 2,6-DMC were also blocked by idazoxan but not rauwolscine (Smyth & Li, 1991), indicating that 2,6-DMC and moxonidine may be acting at the same site and/or receptor.

Rilmenidine has at least a 3 fold greater affinity for I₁ non-adrenoceptor, imidazoline receptors than for α_2 -adrenoceptors (Gomez *et al.*, 1991; Ernsberger *et al.*, 1992) and the cardiovascular action of central administration of rilmenidine was blocked by idazoxan (Feldman *et al.*, 1990). The present study demonstrated that, like moxonidine (Allan *et al.*, 1993) and 2,6-DMC (Smyth *et al.*, 1992a), rilmenidine increased urine flow rate and sodium excretion in a dose-related fashion. Similarly, the increase in flow rate was associated

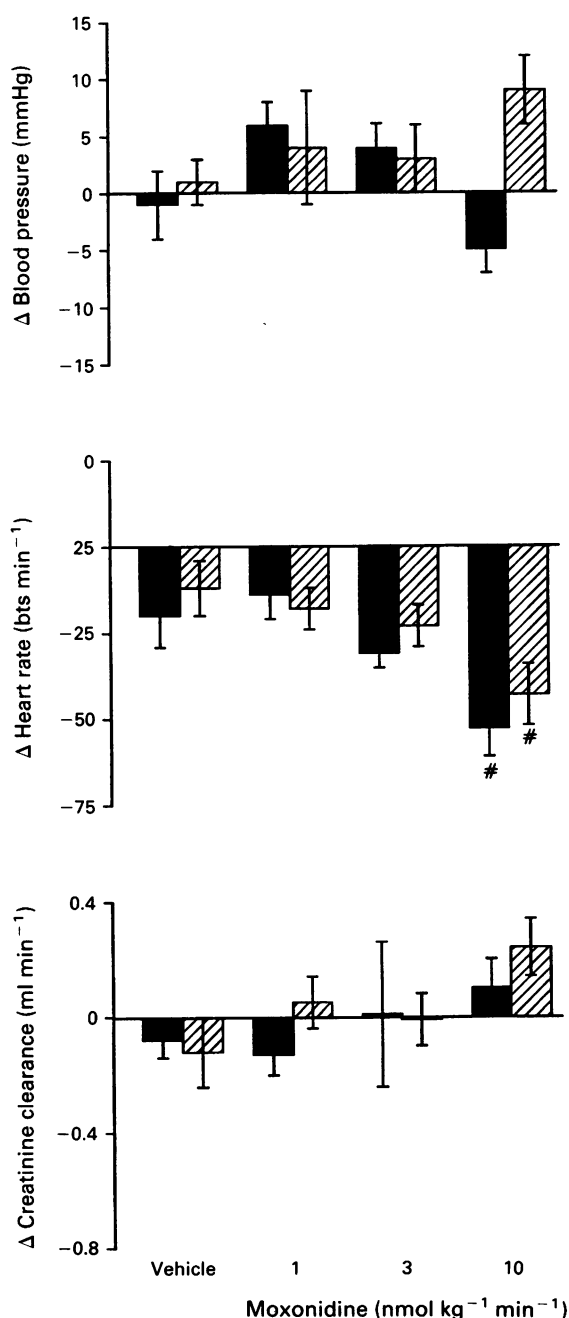


Figure 4 The effects of moxonidine on mean arterial blood pressure, heart rate and creatinine clearance. The solid columns represent the 1K-sham rats and the hatched columns represent the 1K-1C hypertensive rats. *denotes $P < 0.05$ between 1K-sham normotensive and 1K-1C hypertensive rats. #denotes $P < 0.05$ as compared with the respective control group.

with an increase in osmolar clearance rather than an increase in free water clearance as has been documented for α_2 -adrenoceptor agonists (Blandford & Smyth, 1990; Gellai, 1990). This similarity of 2,6-DMC with moxonidine and rilmenidine would be consistent with 2,6-DMC acting at the same site, i.e. the non-adrenoceptor, imidazoline receptor. However, radioligand binding studies will be required to support this contention.

In the present study, the renal effects of rilmenidine and moxonidine were significantly attenuated in 1K-1C hypertensive rats as compared with 1K-sham normotensive rats. These results were similar to those found for 2,6-DMC in 1K-1C hypertensive rats (Li & Smyth, 1994). It is important

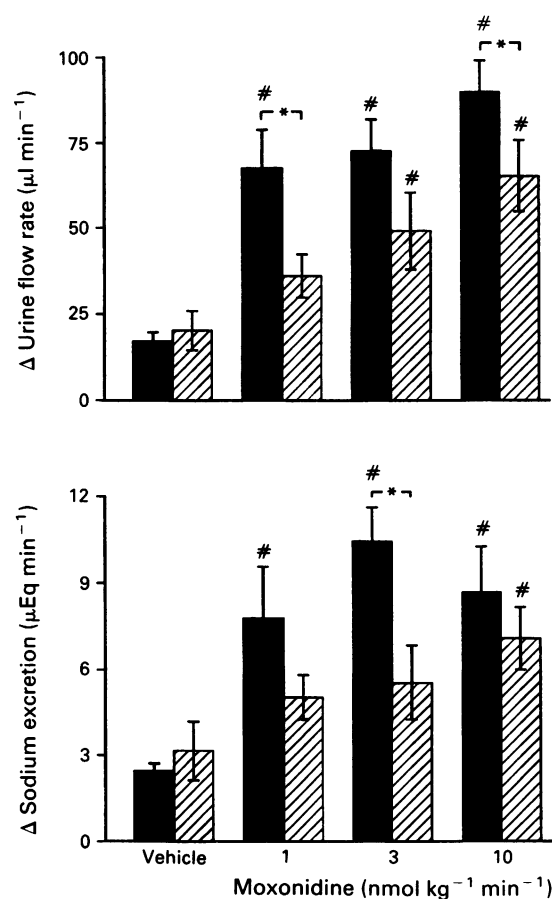


Figure 5 The effects of moxonidine on urine flow rate and sodium excretion. The solid columns represent the 1K-sham rats and the hatched columns represent the 1K-1C hypertensive rats. *denotes $P < 0.05$ between 1K-sham normotensive and 1K-1C hypertensive rats. #denotes $P < 0.05$ as compared with the respective control group.

to note that this decrease in response to non-adrenoceptor, imidazoline agonists may be specific since the natriuretic response to an α_2 -adrenoceptor agonist (Li & Smyth, 1994) and a V_2 vasopressin receptor antagonist (Li & Smyth, 1993) were not found to be altered in 1K-1C hypertension.

During the chronic phase of 1K-1C hypertension, blood pressure is maintained by an excess of water and sodium retention (Zandberg, 1984; Nabel *et al.*, 1985). Conceivably, the attenuated effects of renal imidazoline receptor stimulation in 1K-1C hypertensive rats could contribute to the sodium and water retention and may be caused by one of two factors. First, an increase in the endogenous levels of the non-adrenoceptor, imidazoline receptor agonist could result in a decrease in the number of these receptors available (receptor occupation) which would decrease the response to the exogenous non-adrenoceptor, imidazoline receptor agonists. At present, the endogenous agonist for non-adrenoceptor, imidazoline receptors has not been determined. However, recent studies suggest that clonidine-displacing substance may be the endogenous non-adrenoceptor, imidazoline receptor agonist (Atlas, 1991; Regunathan *et al.*, 1991). Second, this decreased response may represent a decrease in receptor activity. Insel & Motulsky (1988) found that α_2 -adrenoceptors in tissues such as those in rat kidney may be down- or up-regulated. Antagonists induced an up-regulation and agonists mediated a down-regulation of α_2 -adrenoceptors in spontaneously hypertensive rats, DOCA-salt hypertensive rats and New Zealand Genetically Hypertensive rats (Saiz *et al.*, 1987; Sanchez *et al.*, 1989; Smyth *et al.*, 1992b). The I_1

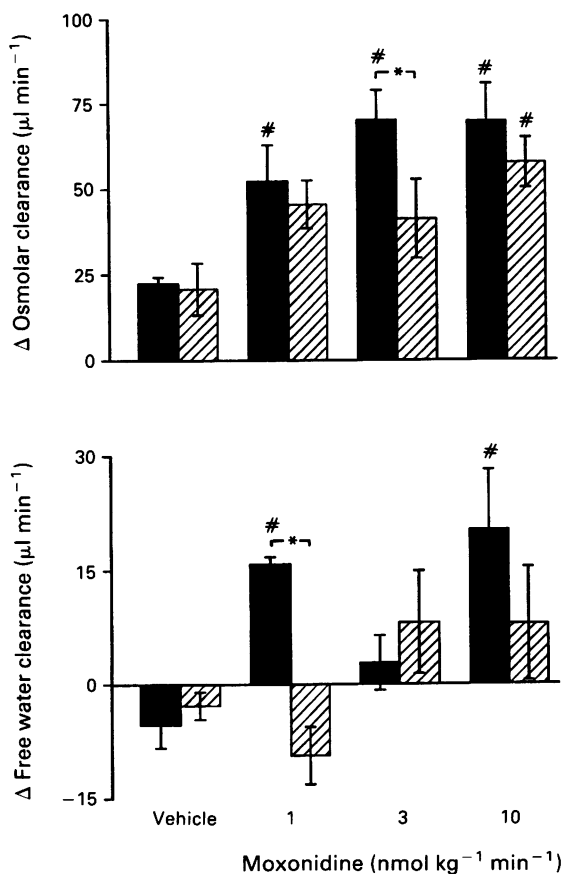


Figure 6 The effects of moxonidine on free water clearance and osmolar clearance. The solid columns represent the 1K-sham rats and the hatched columns represent the 1K-1C hypertensive rats. *denotes $P < 0.05$ between 1K-sham normotensive and 1K-1C hypertensive rats. #denotes $P < 0.05$ as compared with the respective control group.

non-adrenoceptor, imidazoline receptor may also undergo similar regulation. An infusion of angiotensin II produced an up-regulation of I_1 sites (Ernsberger *et al.*, 1991). Similarly, although the receptor subtype was not described, Olmos *et al.* (1992) demonstrated that chronic treatment with idazoxan or cirazoline (imidazoline compounds) increased the density of non-adrenoceptor, imidazoline receptors in the brain of Wistar Kyoto and Sprague-Dawley rats but not spontaneously hypertensive rats. The altered non-adrenoceptor, imidazoline receptor number/activity may be secondary to increased agonist levels (clonidine-displacing substance) or a pathophysiological decrease in receptor activity. Recent studies in our laboratory have shown that [^3H]-idazoxan binding was decreased in kidneys of 1K-1C hypertensive rats compared with 1K-sham normotensive rats. Conversely [^3H]-rauwolscine binding was similar in 1K-1C hypertensive and 1K-sham normotensive rats (Li & Smyth, 1994). This decrease in sites labelled by [^3H]-idazoxan in 1K-1C kidneys would be consistent with the decrease in response to non-adrenoceptor, imidazoline agonists reported in the present study.

In summary, the renal effects of rilmenidine were completely attenuated and the renal response of moxonidine was significantly decreased in 1K-1C hypertensive rats compared with the response in 1K-sham normotensive rats. This attenuation indicated that the activity of renal I_1 non-adrenoceptor, imidazoline receptors was decreased. Whether the decrease in activity of this natriuretic I_1 non-adrenoceptor, imidazoline receptor contributes to the increase in blood pressure in this 1K-1C acquired model of hypertension remains to be determined.

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