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Chronic prazosin attenuates the natriuretic response to a modest saline load in anaesthetized rats

S. Brian Penner & [1]Donald D. Smyth

Depts. Pharmacology & Therapeutics and Internal Medicine, University of Manitoba, 770 Bannatyne Ave., Winnipeg, Manitoba, Canada R3E OW3

1 The effect of chronic prazosin pretreatment (3 days) on the ability to excrete a modest saline load (i.v. saline, 0.097 ml min^{-1}) was studied in the anaesthetized rat. Three days before the experiment, the drinking water was replaced with 0.5% dextrose (control), 0.015 mg ml^{-1} prazosin in 0.5% dextrose (low dose) or 0.15 mg ml^{-1} prazosin in 0.5% dextrose (high dose).

2 The selectivity of the prazosin for α_1-adrenoceptors was evaluated in pithed rats. The pressor response to phenylephrine was partially attenuated by the low dose of prazosin and completely attenuated by the high dose of prazosin. The pressor response to clonidine was slightly decreased by the 3 day prazosin pretreatment indicating a selectivity for α_1-adrenoceptors.

3 In rats pretreated with the low dose of prazosin, there was a significant decrease in sodium and water, but not potassium excretion as compared to the control group. Captopril failed to alter these effects of the low dose of prazosin. Blood pressure and creatinine clearance were the same in both groups. In rats pretreated with the high dose of prazosin, there was a further decrease in sodium and water but not potassium excretion. However, this dose of prazosin also significantly decreased blood pressure and increased creatinine clearance. A decrease in renal perfusion pressure with an aortic clamp to the same level as that observed with the high prazosin dose also decreased sodium and water but not potassium excretion. The decrease in sodium and water excretion was not as great as that observed with the high dose of prazosin.

4 The results indicate that chronic α_1-adrenoceptor blockade with prazosin attenuates the ability to excrete a saline load in a dose-related manner. Whether this inability to excrete a saline load is analogous to the sodium and water retention observed with the clinical use of prazosin remains to be determined.

Introduction

Previous studies have demonstrated that activation of renal α-adrenoceptors will increase sodium retention (DiBona, 1982), whereas renal denervation will increase sodium and water excretion (DiBona & Sawin, 1983; Rogenes & Gottschalk, 1982). Recent studies in the dog (Osborn *et al.*, 1983), rabbit (Hesse & Johns, 1984) and rat (Smyth *et al.*, 1985) have identified the α_1-adrenoceptor as the receptor subtype mediating this sodium and water retention induced by renal nerve stimulation.

α_1-Adrenoceptor antagonists have been used in the treatment of high blood pressure (Graham & Pettinger, 1979). Acute animal experiments would suggest that blockade of the renal α_1-adrenoceptors, which mediate sodium and water retention, should be associated with a natriuresis (Osborn *et al.*, 1983; Hesse & Johns, 1984; Smyth *et al.*, 1985). α_1-Adrenoceptor blockade with prazosin has not been associated clinically with an increase in electrolyte excretion but an increase in sodium and water retention (Koshy *et al.*, 1977; Izzo *et al.*, 1981; Stanaszek *et al.*, 1983; Bauer *et al.*, 1984) which may limit its antihypertensive effects.

In normal and hypertensive rats, the ability to excrete a saline load has been associated with a subsequent reduction in renal nerve activity (Ricksten *et al.*, 1981; DiBona & Sawin, 1985) and consequently a decreased activation of α_1-adrenoceptors. In the presence of a high level of renal nerve activity (i.e. low sodium intake), the greater reduction of renal nerve activity following a saline load would result in an enhanced natriuresis as compared to situations (i.e. high sodium intake) where nerve activity is suppressed (DiBona & Sawin, 1985).

[1]Author for correspondence.

We therefore studied the ability of normal rats to excrete a mild saline load in the presence of varying degrees of α_1-adrenoceptor blockade with prazosin. The level of renal α_1-adrenoceptor activation (i.e. effective renal nerve activity) appears to play an important role in determining the natriuretic response to a saline load. Thus, in the presence of an α_1-adrenoceptor antagonist, the response to a saline load should be attenuated. The present results suggest that the ability of the kidney to excrete a saline load is dependent on the presence of functional renal α_1-adrenoceptors. Whether this inability to excrete a saline load following prazosin treatment is related to the sodium and water retention observed with prazosin treatment clinically remains to be determined.

A preliminary account of this work was presented at the 37th Annual Fall Meeting of the American Physiological Society (Smyth *et al.*, 1986a).

Methods

Animal pretreatment

Sprague Dawley rats (280–320 g) were prepared by a method previously described by Roman & Cowley (1985) and modified in the present study which allowed the study of renal function *in vivo*. Rats were unilaterally nephrectomized (right kidney), under ether anaesthesia, 10 days before the experimental day. Three days prior to the experimental day, the rats were randomly divided into three groups. In the control group, the distilled drinking water was replaced with 0.5% dextrose (w/v). The other two groups of rats received 0.015 or 0.15 mg ml^{-1} of prazosin in the 0.5% dextrose drinking water. Standard laboratory diet (0.45% sodium dry weight) was used at all times.

Experimental procedure

On the day of the experiment, rats were anaesthetized with pentobarbitone (Nembutal, BDH; 60 mg kg^{-1}, i.p.). Additional anaesthetic was administered in bolus doses of 3 mg kg^{-1} intravenously as required through the experiment. A tracheotomy was performed and the animals placed on an artificial ventilator (60 strokes min^{-1}, 2 ml). Body temperature was maintained (38°C) with a small animal heating blanket and a rectal thermometer connected to a Harvard Animal Blanket Control Unit. A polyethylene catheter (PE60) was placed in the left carotid artery and blood pressure recorded with a Statham pressure transducer (Model P23Dc) connected to a Grass polygraph Model V. Two catheters were placed in the jugular vein for the variable infusion of saline or the α_1- and α_2-adrenoceptor agonists phenylephrine or clonidine (see below). At this point the preparation was used for either the determination of pressor responsiveness or the *in vivo* renal response to a saline load.

Pressor response to clonidine and phenylephrine Following the surgical procedure, the animals were pithed by the insertion of a needle in the right orbit and advancement of the needle down the spinal column. The preparation was allowed to stabilize for 30 min. The selectivity of blockade by the prazosin pretreatment for α_1-adrenoceptors was determined by the recording of the pressor response to incremental infusion rates of an α_1-adrenoceptor agonist, phenylephrine (0.1, 0.3, 1, 3, 10, 30 and 100 μg kg^{-1} min^{-1}), and an α_2-adrenoceptor selective agonist, clonidine (0.1, 0.3, 1, 3, 10, 30 and 100 μg kg^{-1} min^{-1}). Only one agonist was tested in each rat. Each infusion rate was maintained until a steady state in blood pressure was achieved.

Renal function In a separate group of rats, the effect of the prazosin pretreatment on the natriuretic response to a saline load was determined. Immediately following the cannulation of the jugular vein, the right kidney was exposed by a flank incision and the right ureter cannulated with a polyethylene cannula (PE50). Saline was infused i.v. (through a jugular vein catheter) at 0.097 ml min^{-1} to induce a modest diuresis and natriuresis. Following a 45 min stabilization period, 5 consecutive 15 min urine collections were made in preweighed collection tubes. Thus, the urine collection periods were 45 to 60, 60 to 75, 75 to 90, 90 to 105 and 105 to 120 min, after the start of the stabilization. Urine volume was determined gravimetrically. A plasma sample was obtained at the end of the experiment.

Three groups of rats were studied. In the first group of rats (i.e. no prazosin pretreatment), saline was infused at 0.097 ml min^{-1} immediately after the start of the stabilization. This established a mild natriuresis and diuresis. The effect of prazosin pretreatment on this saline (0.097 ml min^{-1})-induced natriuresis and diuresis was then determined in rats pretreated with either 0.015 or 0.15 mg ml^{-1} prazosin in the drinking water for three days before the experiment.

The group receiving the high dose of prazosin had a significantly lower blood pressure than control rats and consequently a decrease in renal perfusion pressure. An additional group of rats was studied in which an aortic clamp was used to decrease the renal perfusion pressure. In this group the experimental procedure was the same as the saline controls except for the placement of a micrometer screw clamp on the abdominal aorta proximal to the renal artery. The femoral artery was cannulated for measurement of the post-occlusion blood pressure. Immediately after sur-

gery, the aorta was partially occluded such that the blood pressure measured in the femoral artery catheter was approximately 100 to 105 mmHg. During the 45 min stabilization period the clamp was adjusted, if necessary, to maintain this level of renal perfusion pressure. The experimental protocol was as previously described.

In another group of rats, the potential role of the renin angiotensin-aldosterone system in the attenuation of the diuresis following prazosin pretreatment was evaluated. Captopril (Capoten, Squibb) was administered daily (5 mg kg^{-1}, i.p.) to rats receiving the low dose of prazosin. On the day of the experiment, the protocol was as previously described.

Plasma and urine sodium and potassium concentrations were determined with a Beckman Klina Flame photometer. Creatinine concentrations were determined by a modified Jaffe method with a Beckman Creatinine Analyzer Model 2 (Yatzidis, 1974).

Statistical analysis were performed with analysis of variance. Duncan's multiple comparison was used to determine the level of significance. Data are expressed as the mean ± standard error of the mean (s.e.mean).

Results

Pressor responsiveness

The effect of the prazosin pretreatment on the pressor response to phenylephrine and clonidine was determined (Figure 1). The prazosin treatment (0.015 and 0.15 mg ml^{-1} in the drinking water) produced a dose-related inhibition of the pressor response to the α_1-adrenoceptor agonist, phenylephrine. The highest dose of prazosin in the drinking water produced an almost complete attenuation of the response to phenylephrine. The response to the α_2-adrenoceptor agonist, clonidine at 10 and 30 $\mu g\,kg^{-1}\,min^{-1}$, was only slightly ($P < 0.05$) altered by either dose of prazosin in the drinking water. Thus, the prazosin treatment was specific for α_1-adrenoceptors.

Effect of chronic α_1-adrenoceptor blockade (3 days) on the renal response to a modest saline load

Saline was infused at 0.097 ml min^{-1} to induce a modest diuresis and natriuresis. In preliminary experiments, this rate of infusion produced a significant increase in urine volume and sodium excretion as compared to rats receiving no infusion or saline infused at 0.024 ml min^{-1}. The effect of the prazosin pretreatment on this saline-induced diuresis and natriuresis was determined. The data are shown in Figures 2 and 3. The data in the second collection period (60–75 min) are representative of the differences observed between groups and will be presented in

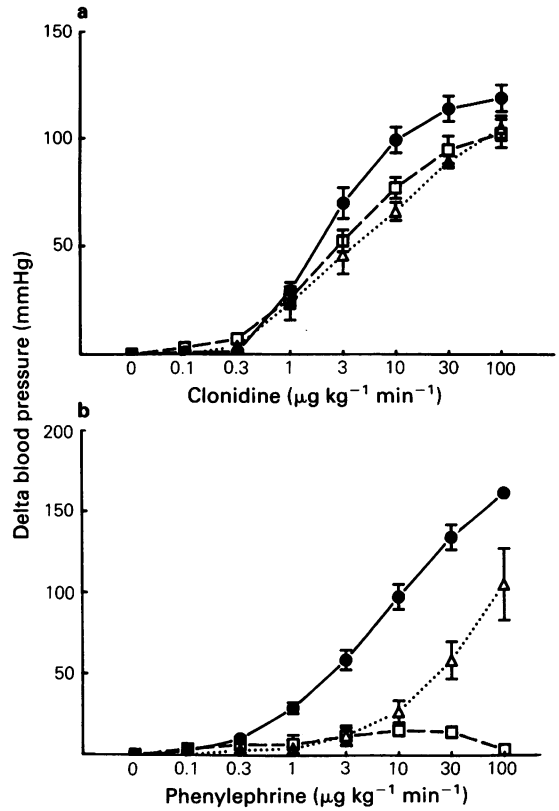

Figure 1 Effect of prazosin in the drinking water for 3 days on the pressor response to clonidine (a) and phenylephrine (b) in the pithed rat; (●) control; (△) prazosin 0.015 mg ml^{-1} in the drinking water; (□) prazosin 0.15 mg ml^{-1} in the drinking water. Values represent the mean of $n = 5$ or more rats per group; s.e.shown by vertical lines.

detail (Table 1). In the group receiving the lower dose of prazosin, there was a significant decrease in the urine volume and the sodium excretion but not the potassium excretion when compared to the control group (Figure 3). This lower dose of prazosin did not alter blood pressure or creatinine clearance (Figure 2). The high dose of prazosin completely blocked the increase in urine volume and the excretion of sodium but not potassium as compared to the control group (Figure 3). However, the high dose of prazosin produced a significant decrease in blood pressure and an increase in creatinine clearance as compared to the control group (Figure 2).

In the aortic clamp experiments, renal perfusion pressure was decreased to a level similar to that observed in rats receiving the high prazosin dose (Table 1). The aortic clamp attenuated the increase in

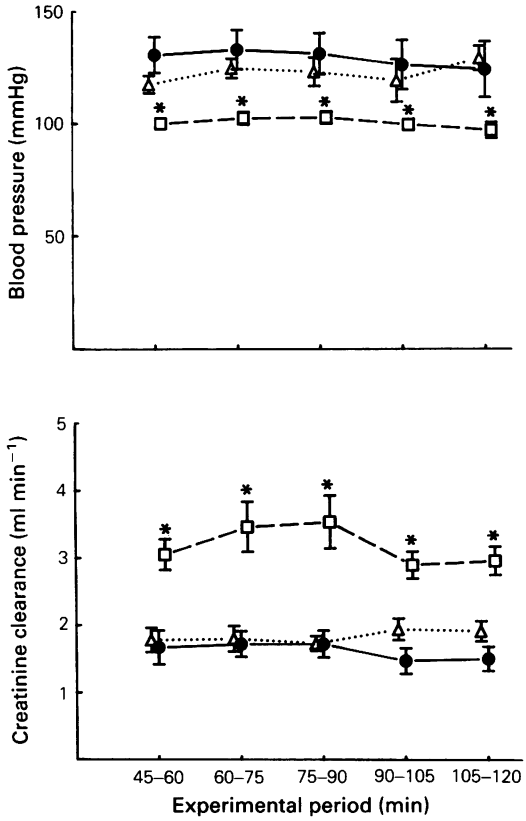

Figure 2 Effect of prazosin pretreatment (3 days) on blood pressure and creatinine clearance during a modest saline load (0.097 ml min^{-1}) in anaesthetized rats: (●) control, (n = 7); (△) prazosin 0.015 mg ml^{-1} in the drinking water (n = 5); (□) prazosin 0.15 mg ml^{-1} in the drinking water (n = 5).
*$P < 0.05$ versus control on all graphs.

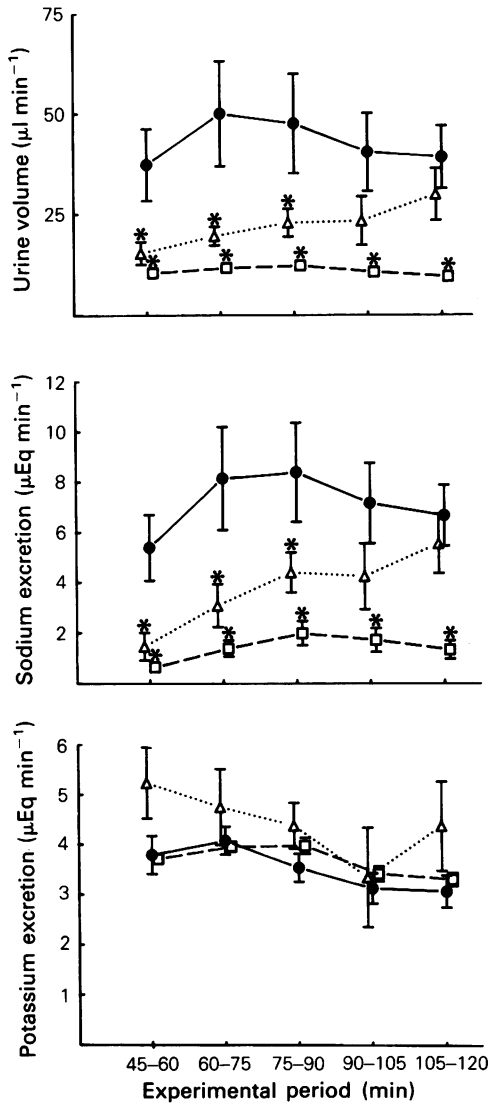

Figure 3 Effect of prazosin pretreatment (3 days) on urine volume and sodium and potassium excretion during a modest saline load (0.097 ml min^{-1}) in anaesthetized rats: (●) control, (n = 7); (△) prazosin 0.015 mg ml^{-1} in the drinking water (n = 5); (□) prazosin 0.15 mg ml^{-1} in the drinking water (n = 5).

urine volume and sodium excretion but not potassium excretion as compared to the control group. This low level of sodium and water excretion was maintained for the duration of the experiment and did not approach the control values. These decreases were not as great as that observed in the rats receiving the high dose of prazosin.

The further addition of captopril to the low dose prazosin treatment produced a significant decrease in blood pressure as compared to the control group but not the group receiving the low dose prazosin alone (Table 1). Captopril failed to alter the creatinine clearance, urine volume or the sodium and potassium excretion as compared to the rats receiving the low dose of prazosin.

Discussion

The role of α_1-adrenoceptors in mediating the anti-natriuretic response to renal nerve stimulation has been well documented (Osborn *et al.*, 1983; Hesse & Johns, 1984; Smyth *et al.*, 1985). These experiments

Table 1 Effect of prazosin pretreatment and aortic clamp on the natriuretic response to a modest saline load in anaesthetized rats

	BP (mmHg)	*Ccr* (ml min^{-1})	*V* (μl min^{-1})	*UNaV* (μEq min^{-1})	*UKV* (μEq min^{-1})
Control ($n = 7$)	132 ± 9	1.72 ± 0.19	49.9 ± 13.1	8.13 ± 2.05	4.08 ± 0.28
Prazosin 0.015 mg ml^{-1} ($n = 5$)	124 ± 4	1.80 ± 0.19	19.5 ± 2.3*	3.07 ± 0.85*	4.75 ± 0.76
Prazosin 0.15 mg ml^{-1} ($n = 5$)	102 ± 3*	3.45 ± 0.37*	11.5 ± 0.8*	1.37 ± 0.32*	3.96 ± 0.10
Aortic clamp ($n = 4$)	105 ± 2*	1.99 ± 0.11	18.1 ± 2.7*	2.14 ± 0.54*	3.88 ± 0.37
Prazosin 0.015 mg ml^{-1} + captopril ($n = 5$)	115 ± 5*	2.65 ± 0.38	18.8 ± 4.1*	2.39 ± 1.07*	4.48 ± 0.71

Values are the means ± s.e. obtained during the second (60–75 min) collection period. Prazosin was given in drinking water; BP, blood pressure; Ccr, creatinine clearance; V, urine volume; UNaV, urine sodium excretion; UKV, urine potassium excretion. In the aortic clamp experiments, the blood pressure measured at the carotid artery was 119 ± 5 mmHg, whereas the post-constriction blood pressure measured at the femoral artery was 105 ± 2 mmHg. In another group of rats, captopril (5 mg kg^{-1}) was administered (i.p.) daily with the prazosin treatment (0.015 mg ml^{-1}).
* $P < 0.05$ vs. saline control.

would suggest that α_1-adrenoceptor blockade should be associated with a natriuretic response. However, chronic treatment with prazosin, even in the absence of a decrease in blood pressure, has been associated with a retention of sodium and water (Koshy *et al.*, 1977; Izzo *et al.*, 1981; Stanaszek *et al.*, 1983; Bauer *et al.*, 1984).

In the present study, prazosin was administered for 3 days by addition to the drinking water. This duration of treatment was chosen since previous studies in rats have demonstrated that the transient decrease in blood pressure observed following an injection of prazosin was attenuated by the third day of treatment (Smyth *et al.*, 1986b). The study of the effect of acute treatment with prazosin may be difficult due to this first dose effect (Graham & Pettinger, 1979). Acute doses of prazosin, similar to that used in the present study, significantly decreased blood pressure (Smyth *et al.*, 1986b; Jeffries *et al.*, 1987). The two levels of prazosin treatment (3 days) used in the present study produced a dose-related blockade to the diuretic and natriuretic response of a modest saline load. A dose-related inhibition of the pressor response to phenylephrine but not clonidine was observed. The slight decrease in the pressor response to clonidine following prazosin is consistent with the ability of clonidine to stimulate α_1-adrenoceptors at high doses. This indicated that α_1- and not α_2-adrenoceptors were blocked by the prazosin pretreatment.

A direct correlation has been reported between the basal level of renal nerve activity and the subsequent natriuresis observed following a saline load in Sprague Dawley rats (DiBona & Sawin, 1985). In rats with a low sodium intake, the level of renal nerve activity was elevated as compared to rats with a high sodium intake (DiBona & Sawin, 1985). The rats on the low sodium intake had a greater decrease in renal nerve activity following a saline load and subsequently a greater increase in sodium and water excretion. In spontaneously hypertensive rats, the enhanced natriuresis observed following a saline load has been attributed to a reduction in the elevated renal nerve activity (Lundin *et al.*, 1984) which has been observed in these rats (Ricksten *et al.*, 1981; DiBona & Sawin, 1986). Renal denervation in these rats produces a significant attenuation of the natriuretic response to a saline load (DiBona & Sawin, 1986). Thus, not only is the presence of renal nerve activity important in determining the natriuretic response to a saline load, but the absolute level of nerve activity is also important.

In the present study, prazosin pretreatment resulted in a dose-related decrease in the natriuresis observed following a modest saline load. This inhibition was directly correlated to the level of blockade of the pressor response to phenylephrine. These results are consistent with the postulate that the natriuretic effect of a saline or water load is dependent on the baseline level of renal nerve activity and consequently renal α_1-adrenoceptor stimulation (DiBona & Sawin, 1985). In our control group, the modest saline load resulted in a significant increase in the excretion of sodium and water. In the animals pretreated with the low dose of prazosin, α_1-adrenoceptors were partially antagonized. The level of activation of the renal α_1-adrenoceptors should have been decreased as compared to the control group. This would have resulted in a lower baseline level of sodium retention induced by renal nerve stimulation and consequently, a decreased res-

ponse to the saline load. In these two groups, blood pressure and creatinine clearance were similar. The decreased excretion of sodium and water following the low dose of prazosin could not be attributed to a decreased renal perfusion pressure. Similarly, in the group receiving the high dose of prazosin, α_1-adrenoceptor function (as determined by the pressor response to phenylephrine) was completely blocked. This absence of functioning α_1-adrenoceptors would be analogous to the denervation studies (i.e. no renal nerve-mediated sodium retention). A failure to excrete a saline load in these rats would be expected since there would be no renal nerve-mediated effects present to be reversed by the saline load. The blood pressure in this group was also significantly decreased which could contribute to the decrease in sodium and water excretion. The experiments with the aortic clamp suggest that the decrease in blood pressure may account for most but not all of the decrease in sodium and water excretion observed in the rats receiving the high dose of prazosin.

Previous studies have also suggested that the enhanced natriuresis observed in spontaneously hypertensive rats (SHR) as compared to Wistar Kyoto (WKY) rats following a saline load may be due to differences in aldosterone levels (Willis & Bauer, 1978). In that study, the attenuated response to a saline load in WKY rats could be reversed by the aldosterone receptor antagonist, spironolactone. Conversely, the enhanced response in the SHR was decreased to levels similar to that observed in the WKY rats by an infusion of aldosterone. In the present study, the attenuated response in the prazosin pretreated rats may have been due to an enhanced level of activity of aldosterone as compared to the control. However, prazosin has been reported to have no effect (Massingham & Hayden, 1975; Graham & Pettinger, 1979) or to decrease plasma renin activity (Preston *et al.*, 1979), indicating aldosterone levels may not be elevated. We combined the prazosin pretreatment with a daily injection of captopril (5 mg kg^{-1}) and in these rats, the response to a saline load in the prazosin pretreatment group versus the prazosin plus captopril treatment group was similar. Thus, varying levels of activity of the renin angiotensin aldosterone system do not appear to play a significant role in the present study.

The discussion so far has centred on an alteration in renal α_1-adrenoceptor functioning following the prazosin pretreatment. The prazosin pretreatment would have resulted in an antagonism of α_1-adrenoceptors in the whole animal. An alternative explanation would be that blockade of venous α_1-adrenoceptors would increase venous capacitance due to a venodilatation (Graham & Pettinger, 1979) and therefore increase the percentage of the total blood volume which is haemodynamically inactive (Greenway & Lautt, 1986). The saline infusion (0.097 ml min^{-1}) which produced the mild diuresis may have not been excreted due to a venous pooling of the infused saline. This postulate, however, is speculative and cannot be substantiated by the present results.

In the present study, renal blood flow was not measured. Previous studies in conscious rabbits have demonstrated that acute injections of prazosin, which decrease blood pressure to an extent similar to or greater than that in the present study, did not alter renal blood flow (Bolt & Saxena, 1984). Clinical studies have shown the absence of changes in renal blood flow despite a significant decrease in blood pressure (Bauer *et al.*, 1984). However, these results cannot be directly compared to the anaesthetized rat. Since we did not measure renal blood flow directly, the changes produced by prazosin may be intra or extrarenal and further, more refined methods will be needed to distinguish these possibilities.

Finally, in the group receiving the high dose of prazosin, the creatinine clearance was found to nearly double in value. The three groups of rats studied were done in a random order. Thus, the increased creatinine clearance could not be attributed to a systematic error in sequence of the experiments. We have also conducted studies with acute prazosin treatment in rats receiving the same saline load. In rats receiving a bolus dose of prazosin (0.01 mg kg, i.v.), the creatinine clearance was again found to be nearly doubled in the presence of the saline load (Penner *et al.*, 1987). The reason for these unanticipated observations is unknown.

In summary, chronic α_1-adrenoceptor blockade with prazosin, at a dose that did not decrease blood pressure, significantly decreased the ability of the kidney to excrete a modest saline load. The present results are consistent with the postulate that the level of excretion of a saline load is dependent on functioning α_1-adrenoceptors. This failure to excrete a saline load following α_1-adrenoceptor blockade may be related to the retention of sodium and water observed with the clinical use of prazosin.

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