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Effect of rilmenidine on arterial pressure and urinary output in the spontaneously hypertensive rat

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Abstract

Rilmenidine is an antihypertensive agent acting at the imidazoline receptor that may have both central effects in the ventral lateral medulla and direct effects on the kidney to alter Na^+ excretion. The present experiments examined whether rilmenidine induces a leftward shift or change in the slope of the pressure-natriuresis curve in the spontaneously hypertensive rat (SHR). A single oral gavage dose indicated that 3 and 10 mg/kg rilmenidine significantly lowers arterial pressure at 4–12 h after administration by oral gavage. The effect of rilmenidine on pressure-natriuresis was studied using twice daily doses of 1 and 3 mg/kg for control and treated SHR drinking tap water or 1% NaCl for 3 days. Na^+ excretion was measured over 24 h, and mean arterial pressure was measured 6–8 h after the morning dose of rilmenidine. The results indicate that 1 mg/kg had no effect, while the pressure-natriuresis relationship for the rats receiving the 3 mg/kg dose was shifted to the left and was not significantly different from the vertical slope of the untreated SHR. This experiment also suggested that rilmenidine may attenuate the salt preference of the rats. This was confirmed in an additional series of experiments in which the rats had access to both tap water and 1% NaCl. Thus, rilmenidine shifts the pressure-natriuresis relationship to the left and reduces salt preference in SHR. © 1997 Elsevier Science B.V.

Keywords: Pressure-natriuresis; Imidazoline; Salt preference; Oral gavage

1. Introduction

There are two major subclasses of imidazoline receptors that have been designated as the I_1 and I_2 sites (Ernsberger et al., 1987, 1993; Michel and Insel, 1989). The I_1 receptor has been implicated in antihypertensive mechanisms of imidazoline receptor agents (Ernsberger et al., 1990c; Gomez et al., 1991; Tibiriça et al., 1991). This receptor has a restricted distribution in the brain with sites in the ventrolateral medulla, hippocampus, hypothalamus and striatum (Ernsberger et al., 1987; Kamasaki et al., 1990). In addition, the I_1 receptors are likely situated on neurons in the brain since they are not found in cultured astrocytes (Ernsberger et al., 1990b). Considerable evidence has demonstrated that the I_1 receptor sites in the ventral lateral medulla cause acute decreases in arterial pressure and suggest that they are responsible for the antihypertensive action of imidazolines such as clonidine and the oxazolamine, rilmenidine (Dubar and Pillion, 1995; Gomez et al., 1991; Reis et al., 1989; Tibiriça et al., 1991). These agents presumably bind to imidazoline receptors in the ventral lateral medulla to inhibit sympathetic nerve discharge and lower arterial blood pressure (Gomez et al., 1991; Head and Sannajust, 1992; Sannajust et al., 1992a).

Imidazoline binding sites are also located in the kidney (Ernsberger et al., 1990a; MacKinnon et al., 1993; Michel et al., 1989) and they were originally thought to be primarily of the I_2 subclass (Coupry et al., 1989; Ernsberger et al., 1990a). However, other investigations have suggested direct actions of I_1 receptors in the kidney mediating increases in urine flow and Na^+ excretion (Allan et al., 1993; Penner and Smyth, 1994; Smyth and Penner, 1995) and I_1 binding sites have been demonstrated in the kidney (Ernsberger et al., 1990a, 1993; Gargalidis-Moudanos and Parini, 1995; Hamilton et al., 1993). It has not been established whether these renal imidazoline receptors have a role in the antihypertensive action of compounds such as

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rilmenidine; however, the long-term control of arterial pressure involves renal mechanisms that maintain salt and water balance. The relationship of Na^+ excretion to the arterial pressure (pressure-natriuresis) is thought to be a critical intrinsic link for maintaining an arterial pressure set-point (Cowley, 1992). Previously, changes in the position and slope of the pressure-natriuresis relationship (also called the renal function curve) have been used to characterize antihypertensive drugs in basic research (Kline and Mercer, 1987).

Pressure natriuresis can be modulated by neuronal, hormonal and local mechanisms (Cowley, 1992; Hall et al., 1980). It would be expected that antihypertensive drugs would affect one of these three variables resulting in an increased ability of the kidney to excrete Na^+ and water at a given level of arterial pressure. This is seen as a change of position or slope of the renal function curve. This would allow fluid balance to be achieved at lower steady-state levels of arterial pressure. A previous investigation did not observe Na^+ retention when arterial pressure was lowered with rilmenidine in hypertensive subjects (Safar, 1989), which would suggest that rilmenidine produced a leftward shift in the renal function curve. Rilmenidine may have direct effects at both the ventral lateral medulla, resulting in sympathoinhibition and subsequent vasodilation, and the kidney, resulting in increased Na^+ excretion. In addition, rilmenidine has been shown to increase Na^+ excretion indirectly in anesthetized rats, by a mechanism involving the renal nerves (Kline and Cechetto, 1993; Kline et al., 1994).

The present experiments were designed to characterize the shift in the renal function curve produced by rilmenidine in spontaneously hypertensive rats (SHR). There were three series of experiments. The first series of experiments examined changes in mean arterial pressure and heart rate continuously for 12 h and again at 24 h following a single 1, 3 or 10 mg/kg dose administered by oral gavage to conscious, chronically instrumented SHR. Based on these results, a second series examined the effect of rilmenidine on the renal function curve in response to twice daily doses of the drug while monitoring arterial pressure 6–8 h after the morning administration of the drug. The results from the second series suggested that rilmenidine may attenuate the salt preference of the rats. Therefore, in a third series of experiments this question was examined by offering control and treated rats both tap water and 1% NaCl.

2. Materials and methods

2.1. Continuous cardiovascular monitoring following a single dose

To determine the time course and effective dose of the antihypertensive effect of rilmenidine, we examined changes in mean arterial pressure and heart rate for 12 h continuously and again at 22–24 h following a single 1, 3 or 10 mg/kg dose administered by oral gavage to conscious, chronically instrumented SHR. SHR (Harlan Sprague-Dawley, MN, USA) 11–13 weeks of age were anaesthetized with pentobarbital (40 mg/kg, i.p.) and maintained under anaesthesia with supplemental doses (20 mg/kg, i.v.). The right femoral artery was cannulated for the measurement of arterial blood pressure. The catheters were filled with a saline solution containing heparin (1000 units per ml). The catheter was securely sutured in place and tunneled subcutaneously to the dorsal aspect of the neck. The antibiotic, Pen-Di-Strep (0.2 ml, i.m.) was administered after surgery to prevent infections. Six days after recovery from surgery the femoral arterial catheter was connected to a Statham P23D volumetric pressure transducer and mean arterial pressure was monitored on a Grass polygraph. Heart rate was determined from the pulse pressure using a Grass tachograph. A baseline recording of arterial pressure and heart rate was obtained for 2 h. Rilmenidine (1, 3 or 10 mg/kg in 0.1 ml tap water or tap water alone) was given via oral gavage and the recording continued for a further 12 h. The following day, 22–24 h after the rilmenidine administration, the cardiovascular variables were monitored again for a 2 h period. Mean arterial blood pressure and heart rate for each hour were determined from the average of 6 recordings from each hour. Statistical significance was tested for all changes using analysis of variance (ANOVA) and Dunnett multiple comparison's tests with a $P < 0.05$ indicating significant differences.

2.2. Arterial pressure-urinary output relationship

Similar to the first series of experiments, SHR (11–13 weeks of age) were anaesthetized and prepared with chronic femoral artery catheters for the measurement of arterial pressure. The rats were then placed in metabolic cages and allowed 6 days for recovery.

Three groups of SHR then received either 1 mg/kg rilmenidine, 3 mg/kg rilmenidine or a control gavage every 12 h. Three days after the start of the drug or control gavage each of these three groups was divided into two subgroups. One subgroup was placed on 1% NaCl drinking solution (to Na^+ load the animals) while the other continued to drink tap water throughout the experiment. On day 3 (after the start of the drug and before the change in the salt diet) and day 6 (3 days after the change in salt diet) 24 h collections of fluid and food intake, urine output and Na^+ and K^+ excretion were measured. Urinary Na^+ and K^+ concentration were measured with a flame photometer (Radiometer, Copenhagen, Denmark) and used to calculate Na^+ and K^+ excretion. On days 3 and 6, the arterial pressure and heart rate were monitored for 2 h between 6–8 h after the morning drug administration. Mean arterial pressure was calculated using 10 values for each hour of recording.

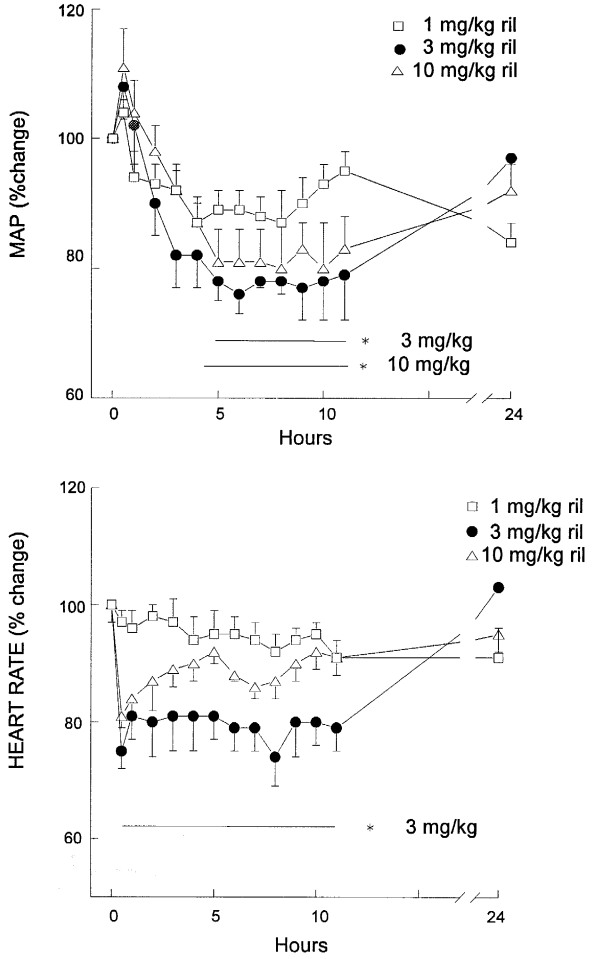

Fig. 1. Mean arterial pressure (MAP) and heart rate (HR) changes as a percent of initial blood pressure or heart rate in SHR following 1 mg/kg ($n = 6$), 3 mg/kg ($n = 5$) and 10 mg/kg ($n = 6$) rilmenidine treatment by oral gavage. MAP and HR were recorded continuously for 12 h after the drug administration and at 24 h. ———— * indicates the times when the arterial pressure or heart rate were significantly lower than initial values.

The 3-day 1% NaCl drinking solution regimen is sufficient to obtain steady state and has been used to show changes in renal function curves in rats with arterial pressure measured by telemetry (Dr. M. Adams, personal communication). To construct renal function curves, data for 24 h urine output and urinary Na^+ excretion were plotted against the mean arterial pressure during tap water and 1% NaCl conditions (Kline and Mercer, 1987). Statistical significance was tested for all changes using ANOVA and Neuman-Keuls tests with a $P < 0.05$ indicating significant differences.

2.3. Effect of rilmenidine on Na^+ chloride preference in SHR

In the second series of experiments the rats which were given rilmenidine had a reduced intake of NaCl when compared to the controls. Previous investigations have demonstrated that idazoxan increases food and water intake via a non-adrenoceptor site (Jackson et al., 1991; Jackson and Nutt, 1992), while α_2- adrenergic stimulation can also increase food and water intake (Goldman et al., 1985; Leibowitz, 1980; Sanger, 1983). However, it is not likely that rilmenidine in the present experiments was having a similar effect since the amount of tap water ingested by the rilmenidine group was not significantly different from the control group on tap water. Another possibility was that rilmenidine was affecting the salt preference of these hypertensive rats.

In this series of experiments there was no surgery for implantation of arterial cannulas. The rats were placed in metabolic cages for the collection of urine on a continuous basis and measurement of food and fluid intake. There were two groups of SHR of which one received 3 mg/kg rilmenidine twice daily by oral gavage while the other received a control oral gavage. For the first 3 days the rats had access only to tap water, while on days 4–6 they had equal access to both tap water and a 1% solution of NaCl. Each day, 24 h levels of fluid and food intake were measured.

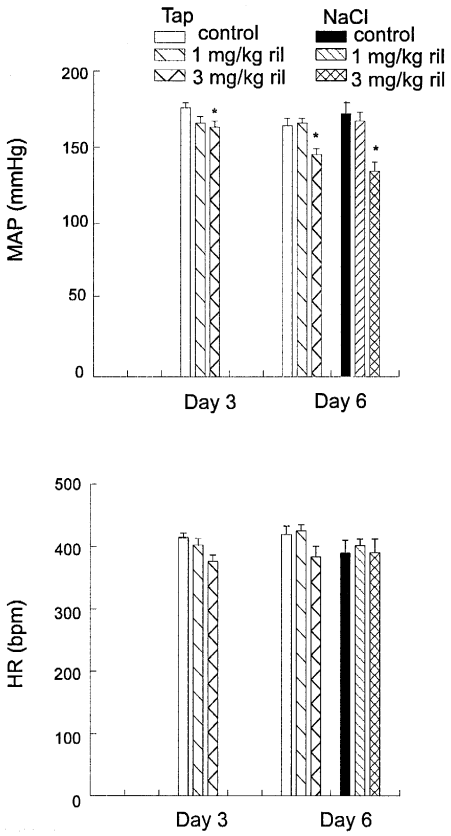

Fig. 2. Mean arterial pressure and heart rate of SHR during control and 1 mg/kg and 3 mg/kg rilmenidine treatment. All animals were given tap water for 3 days (Tap) and either tap water or 1% NaCl solution for the last 3 days (NaCl). First 3 days: control, $n = 11$; 1 mg/kg, $n = 11$; 3 mg/kg, $n = 16$. Last 3 days: control Tap, $n = 6$; control NaCl, $n = 5$; 1 mg/kg Tap, $n = 6$; 1 mg/kg NaCl, $n = 5$; 3 mg/kg Tap, $n = 6$; 3 mg/kg NaCl, $n = 10$. * Significant difference from control.

3. Results

3.1. Time course of cardiovascular effects of rilmenidine following a single oral dose

The acute effects of administration of rilmenidine on mean arterial pressure and heart rate are shown in Fig. 1. A dose of 1 mg/kg rilmenidine (p.o.) elicited approximately a 20 mmHg decrease in mean arterial pressure at 4–8 h after administration, from initial values of 167 ± 5 mmHg. The arterial pressure recovered at 9–12 h after the drug administration. However, ANOVA did not indicate that there were any significant differences in these values. There was no change from initial (427 ± 12 bpm) in the heart rate with the 1 mg/kg dose. Beginning at 5 h to 12 h (the end of the continuous recording period) after the administration of the drug there was a significant decrease in arterial pressure (approximately 35 mmHg) from an initial value of 142 ± 4 mmHg for the 3 mg/kg dose. However, the arterial pressure had recovered by 24 h after the drug. Heart rate also was considerably reduced from initial (386 ± 12 bpm) during this same time. The 10 mg/kg dose of rilmenidine resulted in a 30 mmHg decrease in arterial pressure from 4 to 12 h after rilmenidine administration from an initial level of 148 ± 3 mmHg. The arterial pressure had recovered at 24 h. Heart rate also was reduced from the initial (322 ± 46 bpm) more than 20% for the first hour but recovered to approximately 10% of the initial for the rest of the 24 h period. In all rilmenidine groups there was an initial brief increase (less than 30 min) in arterial pressure that preceded the more prolonged decrease. The initial values for a group of control animals were 168 ± 8 mmHg and 389 ± 9 bpm ($n = 4$) and these did not change significantly throughout the recording period (data not shown).

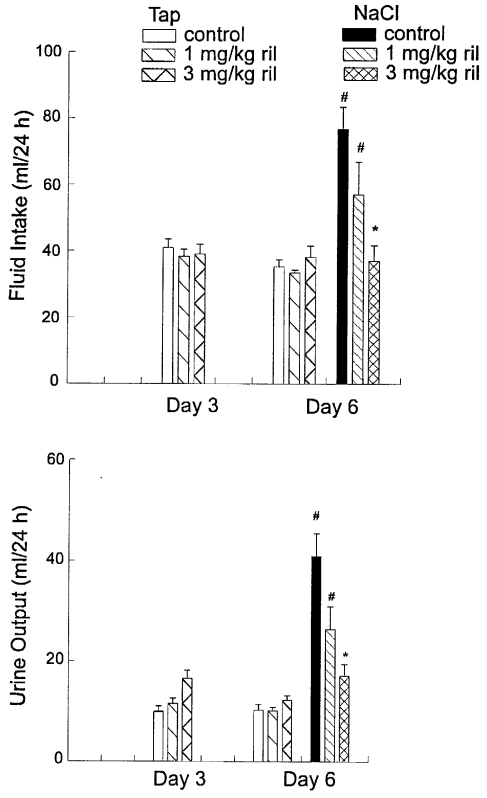

Fig. 3. Fluid intake and urine output over 24 h of SHR during control and 1 mg/kg and 3 mg/kg rilmenidine treatment. All animals were given tap water for 3 days (Tap) and either tap water or 1% NaCl solution for the last 3 days (NaCl). First 3 days: control, $n = 11$; 1 mg/kg, $n = 11$; 3 mg/kg, $n = 16$. Last 3 days: control Tap, $n = 6$; control NaCl, $n = 5$; 1 mg/kg Tap, $n = 6$; 1 mg/kg NaCl, $n = 5$; 3 mg/kg Tap, $n = 6$; 3 mg/kg NaCl, $n = 10$. * Significant difference from control NaCl; # significant difference from the paired group on tap water.

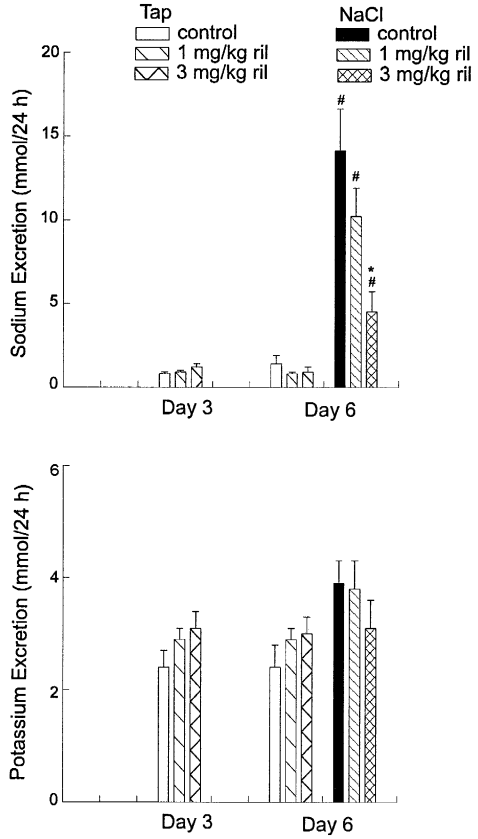

Fig. 4. Na^+ and K^+ excretion over 24 h of SHR during control and 1 mg/kg and 3 mg/kg rilmenidine treatment. All animals were given tap water for 3 days (Tap) and either tap water or 1% NaCl solution for the last 3 days (NaCl). First 3 days: control, $n = 11$; 1 mg/kg, $n = 11$; 3 mg/kg, $n = 16$. Last 3 days: control Tap, $n = 6$; control NaCl, $n = 5$; 1 mg/kg Tap, $n = 6$; 1 mg/kg NaCl, $n = 5$; 3 mg/kg Tap, $n = 6$; 3 mg/kg NaCl, $n = 10$. * Significant difference from control NaCl; # significant difference from the paired group on tap water.

3.2. Effect of rilmenidine on arterial pressure-urinary output relationship

The three groups of rats on day 3 and the six subgroups on day 6 did not differ significantly with respect to body weight or food intake during the experimental period. Fig.

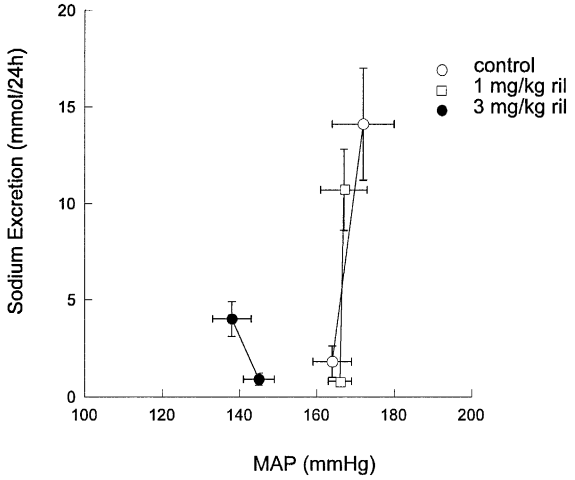

Fig. 5. Arterial pressure–Na^+ output relationships for SHR during control and 1 and 3 mg/kg rilmenidine treatment. All animals were given tap water for 3 days (Tap) and either tap water or 1% NaCl solution for the last 3 days. The arterial pressures of the 3 mg/kg rilmenidine animals were significantly lower than those of the 1 mg/kg animals and the control rats. Last 3 days: control Tap, $n=6$; control NaCl, $n=5$; 1 mg/kg Tap, $n=6$; 1 mg/kg NaCl, $n=5$; 3 mg/kg Tap, $n=6$; 3 mg/kg NaCl, $n=10$.

2 illustrates that the arterial pressure of SHR treated with 3 mg/kg rilmenidine was significantly lower on day 3 and 6 with respect to their respective control group. In addition, on day 6 the 3 mg/kg subgroups were significantly lower than the 1 mg/kg subgroups and significantly lower than the 3 mg/kg group on day 3. The heart rates were not significantly different for all groups on either day 3 or 6 (Fig. 2).

Fig. 3 illustrates that, as expected, the control group on day 6 with 1% NaCl drinking water ingested significantly more fluid than the control group on tap water. However, the rats treated with 3 mg/kg rilmenidine did not exhibit this expected large increase in salt intake and were significantly lower than their controls. The 1 mg/kg group ingested less NaCl solution than the controls and more than the 3 mg/kg group. The fluid intake of the 3 mg/kg rilmenidine group on tap water was similar to that for the control group on tap water. This suggests that the rilmenidine did not non-selectively suppress drinking. The urine output closely paralleled fluid intake (Fig. 3).

Na^+ excretion was elevated in the control group on high salt (Fig. 4). The Na^+ excretion for the 3 mg/kg rilmenidine group on high salt was also significantly elevated compared to the groups on tap water, but was still significantly lower than the high salt control group. The 1 mg/kg group had values intermediate between these two groups. There were no differences observed in the K^+ excretion in any of the groups (Fig. 4).

Fig. 5 is a plot of the Na^+ excretion vs. the mean arterial pressure. The control group had a relatively vertical slope. The 1 mg/kg group had a curve that was nearly

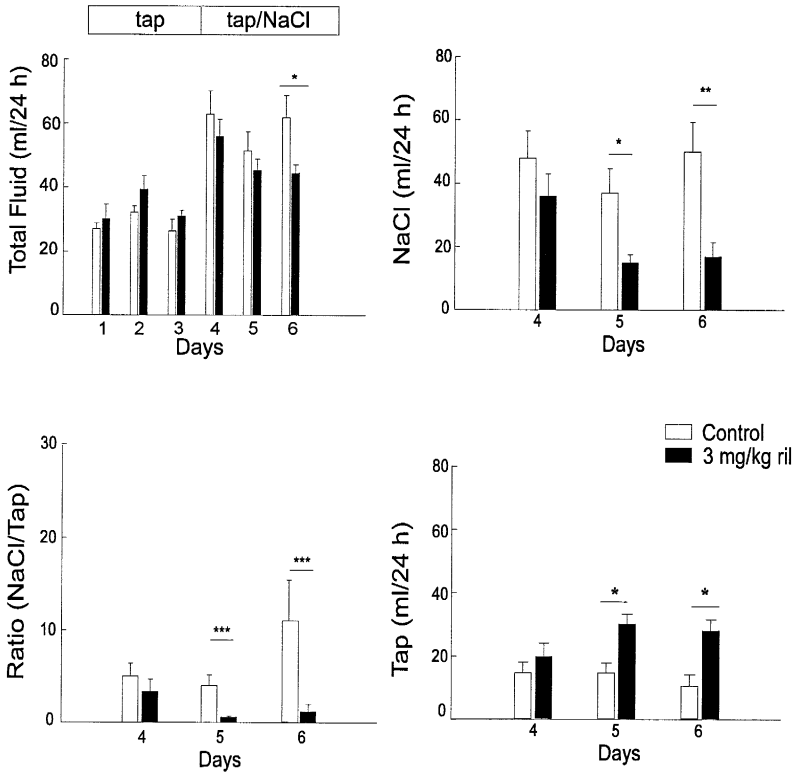

Fig. 6. Total fluid, 1% NaCl solution (NaCl) and tap water (Tap) intake and ratio of NaCl to Tap intake for 24 h in SHR during control ($n=8$) and 3 mg/kg rilmenidine ($n=8$) treatment. The SHR had access to tap water during the first 3 days (tap) and *both* tap water and 1% NaCl solution (tap/NaCl) for the last 3 days.

identical to the controls. Although the 3 mg/kg group did not ingest as much salt as the other two groups, nevertheless the direction and placement of the pressure-natriuresis curve can be determined from the increase in Na^+ excretion that was observed. In this range of the curve, the slope was still steep and the curve was displaced to the left.

3.3. Effect of rilmenidine on Na^+ chloride preference

The body weight and food intake did not differ significantly between the rilmenidine (3 mg/kg, p.o.) and control animals for the 6 days during the drinking preference test. For the first 3 days, when only tap water was available, there was no difference between the control and experimental rats in the fluid intake (Fig. 6). On days 4–6 the control rats drank less tap water than on days 1–3, while the 3 mg/kg rilmenidine group continued to drink similar amounts of tap water on days 4–6 as on days 1–3 (Fig. 6). On days 5 and 6 the rilmenidine group was drinking significantly more tap water than the controls. On days 4–6, the control group began to ingest about 40–50 ml of the 1% NaCl solution daily while the rilmenidine rats on day 4 initially drank a large amount of NaCl solution (36 ± 7 ml) and then smaller amounts (approximately 15 ml daily) of 1% NaCl solution on days 5 and 6 (Fig. 6). Thus, both groups exhibited an increase in total fluid intake on day 4, an increase that was maintained in the control group (Fig. 6). On day 6 the total fluid intake in the rilmenidine group was significantly less than that of the control animals (Fig. 6). The ratio of NaCl solution ingested vs. tap water ingested was considerably higher for the control group than for the rilmenidine group on days 5 and 6 (Fig. 6).

4. Discussion

Our experiments examined the time course of a single oral gavage administration of three doses of rilmenidine over a 24 h period in conscious SHR. In these experiments there was an initial, transient hypertensive phase. This has been observed previously and is thought to be the result of stimulation of peripheral α_1- and α_2-adrenoceptors (Koenig-Bérard et al., 1988; Laubie et al., 1985; Van Zwieten et al., 1986). Following the hypertensive phase, our results clearly indicate that rilmenidine administration by oral gavage at a dose of 3 or 10 mg/kg can effectively lower arterial pressure for up to 12 h after which time there is some recovery of the arterial pressure depending on the dose administered. These results can be compared with previous investigations which indicate that successive i.v. doses of rilmenidine of 0.03, 0.1 and 0.3 mg/kg every 3 h or 0.3, 1.2 and 1.2 mg/kg every 5 h produce significant decreases in arterial pressure (Sannajust et al., 1989, 1992b).

Our results also indicate the effective level of chronic oral gavage rilmenidine treatment in the SHR, since twice daily administration of 3 mg/kg but not 1 mg/kg rilmenidine significantly lowered arterial pressure by the third day of the administration. Furthermore, this treatment appears to have a prolonged effect since the reduction in arterial pressure was not only maintained, but even greater by the sixth day of treatment. A previous investigation in SHR indicated that a dose of rilmenidine even less than this (0.6 mg/kg daily) given orally produced a significant decrease in arterial pressure at 12 weeks but not after 4 weeks of administration (Ghaemmaghami et al., 1990). However, 100 μg/kg/h (s.c.) when continuously infused, effectively reduced the arterial pressure of SHR (Jarrot et al., 1988). In addition, 6 mg/kg in the drinking water but not 1.2 mg/kg was successful in reducing the arterial blood pressure of SHR when administered for 12 days (Sannajust et al., 1989).

The renal function curve for the 3 mg/kg dose, but not the 1 mg/kg dose, was shifted to the left and there was no evidence that the slope was significantly different from the vertical slope of the control. This indicates that, at this dose of rilmenidine, the arterial pressure was relatively insensitive to Na^+ intake. It is important to note that these conclusions regarding the shift to the left apply only to normal and moderate levels of Na^+ intake since it was not possible to obtain high levels of salt loading in the animals on rilmenidine using a 1% NaCl solution for the drinking water.

A significant reduction in slope of the renal function curve has previously been observed for captopril under similar steady-state conditions in the SHR (Kline and Mercer, 1987). As captopril is an angiotensin I converting enzyme inhibitor, this result supported the conclusion that the renal effects of angiotensin II are important in the maintenance of the steep slope of the renal function curve and ensures that the arterial pressure is insensitive to changes in Na^+ intake (Hall et al., 1980). Thus, our data suggest that the 3 mg/kg dose of rilmenidine administered twice daily is not interfering with the renin-angiotensin system.

Previously, a parallel shift to the left in the renal function curve was shown for the vasodilator, hydralazine (Kline and Mercer, 1987). Similarly, in our present experiments the parallel shift of the renal function curve could be due to a rilmenidine-induced sympathoinhibition leading to vasodilation, including the renal vasculature. In addition, a reduction of renal nerve activity would also be expected to shift the renal function curve leftward since renal denervation has been shown to shift the acute pressure-natriuresis curve to the left (Roman and Cowley, 1985). Conversely, administration of norepinephrine intrarenally elicits a shift to the right of the renal function curve (Cowley and Lohmeier, 1979). This potential reduction in renal nerve activity as part of the antihypertensive mechanism is consistent with a great deal of evidence indicating that rilmenidine acutely lowers arterial blood pressure by a reduc-

tion in sympathetic nerve activity via I_1 receptors located mainly in the ventral lateral medulla (Gomez et al., 1991; Reis et al., 1989; Tibiriça et al., 1991). Previously, we have demonstrated an acute decrease in renal nerve activity accompanied by an increase in Na^+ excretion (Kline and Cechetto, 1993). These effects on Na^+ excretion were observed only when the innervation of the kidney was intact under these experimental conditions.

Other reports have indicated that the antihypertensive effect of rilmenidine may also be due to imidazoline receptors located in the spinal cord and ganglia (Sannajust et al., 1992a). Our oral gavage administration would not be able to distinguish between these effects originating from different locations. Furthermore, there is evidence that rilmenidine induces an reduction in the range of the renal sympathetic nerve response to baroreflex activation (Sannajust and Head, 1993). However, other vascular regions such as heart and muscle, which are also influenced by the sympathoinhibitory action of imidazolines, do not show as great a reduction in the range of their response to baroreflex activation following administration of rilmenidine (Muzi et al., 1992; Badoer et al., 1983; Speirs et al., 1990). Whether this selective baroreflex impairment of the renal sympathetic activity is operative in our experiments cannot be determined at present.

In addition, a direct effect of rilmenidine at the renal level would also be expected. It has been demonstrated that rilmenidine is far more selective for I_1 binding sites in isolated proximal tubule cells from the rabbit kidney than for I_2 sites and that rilmenidine poorly interacts with the α_2-adrenoceptors (Gargalidis-Moudanos and Parini, 1995). This selective interaction of rilmenidine with the I_1 binding site may be responsible for the renal effects observed by others (Allan et al., 1993; Smyth and Penner, 1995). It has previously been demonstrated that infusion of monoxidine, an I_1-selective compound, into the renal artery elicits an increase in urine flow that is secondary to an increase in osmolar clearance (Allan et al., 1993). More recently, it has also been demonstrated that intrarenal rilmenidine or agmatine, an endogenous clonidine displacing substance, increases urine flow secondary to an increase in osmolar clearance, primarily composed of Na^+, and this renal effect occurs at doses that do not change arterial blood pressure, creatinine clearance or heart rate (Smyth and Penner, 1995).

The final series of experiments clearly indicate that SHR on rilmenidine have a reduced preference for Na^+ chloride ingestion. Previous reports have indicated that idazoxan can induce an increase in food and water intake at a central non-adrenergic site (Jackson et al., 1991; Jackson and Nutt, 1992) while centrally acting α_2-adrenoceptor agonists can also increase food and water intake (Goldman et al., 1985; Leibowitz, 1980). In addition, injection of clonidine and phenylephrine into the lateral preoptic area of the hypothalamus can reduce the water intake of water-deprived rats (Callera et al., 1993). However, it is not likely, in our experiments, that rilmenidine is affecting the thirst of the SHR for two reasons. In the series of experiments in which the animals were given either normal tap water or 1% NaCl to generate the renal function curve, the rilmenidine groups on tap water or high salt continued to drink the same amount of fluid as the control animals on tap water. In addition, there appeared to be a dose-dependent effect of rilmenidine on saline intake, as the 1 mg/kg dose produced a salt intake that was midway between controls and 3 mg/kg. Secondly, in the salt preference experiments, the rilmenidine-treated animals drank the same amount of tap water for the 6-day period as the controls did prior to the choice of drinking solutions. Only initially did the rilmenidine-treated animals drink the 1% NaCl on day 4, in addition to the tap water, and then reduced their salt intake on days 5 and 6. Thus, these results suggest that rilmenidine attenuated salt preference via a mechanism that does not involve α_2-adrenoceptors. It may involve I_1 receptors in the hypothalamus since these binding sites have been localized to this region of the brain (Kamasaki et al., 1990).

4.1. Summary

These results clearly indicate that a single 3 mg/kg dose of rilmenidine can reduce arterial blood pressure in the SHR for up to 10 h. In addition, 3 mg/kg of rilmenidine administered by oral gavage twice daily can significantly reduce the mean arterial pressure in SHR up to 6 days after the beginning of the drug administration. This dose shifts the renal function curve to the left without producing a change in slope. What is not entirely clear at this time is whether this effect is due exclusively to a central mechanism acting indirectly to enhance Na^+ excretion or if direct effects on the kidney are also implicated. In addition, rilmenidine reduced the high salt intake of these animals without affecting the normal fluid ingestion, suggesting that the drug might be affecting the salt preference of the animal. The last series of experiments, in which the SHR were given a choice of tap water or a high salt solution, indicated that there is a change in gustatory behaviour such that the preference for high salt in the diet is reduced. Thus, rilmenidine may be effective as an antihypertensive agent by increasing the ability of the kidney to excrete Na^+ and maintaining the salt insensitivity to arterial pressure. It may also have a secondary benefit of reducing the salt load to be handled by the kidney. A similar effect of rilmenidine on the salt preference in humans would have beneficial implications for hypertensive patients that are known to be salt sensitive.

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