

ORIGINAL ARTICLES

Experimental Investigations

EFFECT OF CHRONIC TREATMENT WITH ANGIOTENSIN RECEPTOR LIGANDS ON WATER-SALT BALANCE IN WISTAR AND SPONTANEOUSLY HYPERTENSIVE RATS

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ABSTRACT

The renin-angiotensin system plays a crucial role in the regulation of cardiovascular function and maintenance of water-electrolyte balance. The two major receptor types of the system, AT1 and AT2, have different, often opposite effects on these functions.

AIM: To elucidate the impact of long term treatment with selective angiotensin receptor antagonists and an agonist on water-salt balance in normotensive Wistar and spontaneously hypertensive rats (SHRs).

MATERIALS AND METHODS: 12-week-old male Wistar rats and SHRs were individually housed in metabolic cages and 24-h food and water intake and urine and electrolyte excretion were measured. Urinary sodium (UNa), potassium (UK) and chlorine (UCI) were determined by a flame photometer. Losartan, a selective AT1 receptor antagonist, was administered in the Wistar rats and SHRs at a dose of 10 mg/kg/day subcutaneously (sc). Wistar rats were also given the AT2 receptor antagonist, PD123319, subcutaneously at a dose of 10 mg/kg/day. CGP 42112A, an AT2 receptor agonist, was administered intracerebroventricularly in Wistar rats at a dose of 12 µg/rat/day. The drugs were infused continuously for 14 days through osmotic minipumps.

RESULTS: Losartan selectively increased sodium excretion in both rat strains and decreased weight gain in SHRs. PD123319 increased potassium excretion and decreased weight gain in Wistar rats. CGP 42112A increased food and water intake, urine output and UNa⁺ and UK⁺ excretion and decreased weight gain in normotensive Wistar rats.

CONCLUSIONS: Chronic treatment with selective angiotensin receptor ligands modifies water-salt balance in rats through changes both in renal excretory function and ingestive behaviors.

Key words: *angiotensin, losartan, water intake, food intake, PD123319, CGP 42112A, renal excretion, sodium, potassium*

INTRODUCTION

The renin-angiotensin system (RAS) and its main effector, the octapeptide angiotensin (ANG) II play a critical role in the regulation of autonomic activity, cardiovascular function, and maintenance of water-electrolyte balance.¹ Its shorter product, the heptapeptide Ang III, is actually a major effector peptide of the brain RAS, exerting tonic central control over blood pressure in hypertensive animals.² Behavioral and autonomic responses are both necessary to correct water and sodium imbalances

and to maintain body fluid homeostasis. Water and sodium intake are controlled by a forebrain circuitry that involves mostly hypothalamic and limbic areas containing a high density of Ang receptors.³ Circumventricular organs (subfornical organ, organum vasculosum laminae terminalis, and area postrema) represent the main area where Ang and its receptors involved in the control of water and sodium intake and excretion are located.⁴ Circulating and brain born Ang interact with its receptors, and activate a forebrain circuitry involving circumventricular

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organs that project to the medial and lateral hypothalamic nuclei, preoptic nuclei, the septal area, and produce physiological responses.⁵ Ang II and Ang III possess a close affinity to AT1 and AT2 receptor types, but trigger different G-proteins and further different second messengers.⁶ The majority of the physiological actions of the peptides including vasoconstriction, cardiac contractility, increased renal tubule sodium reabsorption, hormone secretion, thirst and salt appetite are mediated by AT1 receptors.⁶ AT1 receptor activation induces an interaction with the G protein, which in turn mediates signal transduction via several effector systems such as phospholipase C, phospholipase D, phospholipase A2, adenylyl cyclase, and ion channels, such as L-type and T-type voltage-sensitive calcium channels. The AT1 receptor is coupled not only to the well recognized Gq-mediated calcium and protein kinase C signaling pathways, but also to intracellular signaling cascades that extend into the nucleus to regulate gene transcription and the expression of proteins controlling growth responses and cell proliferation in several Ang target tissues.

AT2 receptor activation, on the other hand, counteracts the effects of AT1-mediated growth responses in several cell types.⁶ There is increasing evidence that indicates that AT2 receptors exert antagonistic effects including decreased arterial blood pressure and increased urine and sodium excretion.⁷ Spontaneously hypertensive rats (SHRs) develop an imbalance of Ang receptors, in comparison with normotensive controls with a prevalence of the AT1 receptor type and a decrease of AT2 receptors in the renal cortex. This correlates with an inflammatory process and renal injury, and could be associated with the genesis of hypertension in adult SHRs.⁸ The aim of the present study was to investigate the effect of long term treatment with selective Ang receptor antagonists and an agonist on parameters of water-salt balance in normotensive Wistar rats and SHRs.

MATERIALS AND METHODS

ANIMALS AND DRUG TREATMENT

Fifty two male Wistar rats (Breeding House of the Bulgarian Academy of Sciences) and 18 spontaneously hypertensive rats (Medical University, Sofia) were used. All rats were 12 weeks old at the beginning of the study and the SHRs already had established hypertension with an average value of the arterial blood pressure 181 ± 1.45 mm Hg (tail cuff method, Ugo Basile, Italy). The animals were housed individually in metabolic cages in a sepa-

rate room under standardized laboratory conditions: temperature $22 \pm 1^\circ$ C, humidity $60\% \pm 10\%$ and an artificial 12h/12h light (08:00 – 20:00 h) / dark (20:00 – 08:00 h) cycle with light intensity of about 250 lux at the front of the cages. Standard rat diet (0.07 mmol Na⁺/g; 0.16 mmol K⁺/g; 4% water) and tap water were provided ad libitum. PD123319 (Sigma-Aldrich) at a dose of 10 mg/kg/day, for 14 days and losartan potassium (kindly gifted by Merck & Co, Inc.) at a dose of 10 mg/kg/day, were dissolved in sterile isotonic saline and administered for 14 days subcutaneously through osmotic minipumps (Alzet, model 2002), which deliver at 0.5 ml/h. CGP 42112A (Sigma-Aldrich) was dissolved in sterile saline and administered intracerebroventricularly (i.c.v.) by brain kit 2 (Alzet) at a dose of 12 µg/rat/day for 14 days through osmotic minipumps (Alzet, model 2002). The choice of all doses is based on their effects on blood pressure and nociception.^{9,10}

The pumps were inserted s.c. under pentobarbital anaesthesia (Nembutal, Abbott, 40 mg/kg, i.p.) between the scapulae in a small pocket formed using a haemostat, in accordance with manufacturer's instructions. Brain infusion kits were implanted in the right lateral ventricle with coordinates 1 mm lateral and 3 mm posterior to the bregma and 4 mm below the skull surface¹¹ and fixed through screws and dental cement. Control groups were implanted with saline filled pumps. All pumps were removed under pentobarbital anesthesia upon completion of their delivery rate (15 days after the implantation).

All experiments were approved by government authorities in full accordance with EC Directive 86/609/EEC for animal experiments.

EXPERIMENTAL DESIGN

Rats were individually housed in metabolism cages 2 weeks before the start of the experiments for adaptation to the cages and experimenter. Powdered food and tap water were available ad libitum. Body weight (± 1 g) was measured daily between 08:00 and 09:00 h, and 24-h food intake, water intake and urine excretion – 14 days after the start of treatment. All data were calculated per kg of body weight.

Blood pressure was measured between 09:00 AM and 11:00 AM, 13 days after the start of chronic drug administration. All experiments were carried out in autumn (October-November).

WATER-SALT BALANCE

Urinary sodium (UNa), potassium (UK) and chlorine (UCI) were measured with an IL943 Flame Photometer (Instrumentation Laboratories) in mmol/l urine and data were calculated per kg of body weight.

STATISTICAL ANALYSIS

All data are expressed as mean ± SEM. Statistics were performed by one-way ANOVA with Bonferoni post test (long-term drug treatment as factor) or Mann-Whitney for non-parametric analysis with Dunn's post test. P values of less than 0.05 were considered as statistically significant.

RESULTS

CHANGES IN BODY WEIGHT

Table 1 shows body weight gain from the beginning to the end of treatment. In the saline treated Wistar group the weight increased by 34 ± 3.8 g over 14 days, whereas this weight gain was significantly lower in SHR controls (# p = 0.01). Wistar rats treated with losartan did not show any differences in rate of weight gain compared to controls in contrast to chronic PD 123319 and CGP 42112A treatment during which the rats gained much less than controls (p = 0.005). Losartan-treated SHRs showed a significant reduction of weight gain compared to controls (p = 0.04) (Table 1).

MEASUREMENT OF FOOD AND WATER INTAKE

SHR controls consumed significantly less food during the 14 days period of infusion in comparison with Wistar controls (F1, 41 = 7.26, p = 0.01). Long-term treatment with AT1 and AT2 receptor blockers losartan and PD123319, respectively did not change the food intake, however AT2 receptor agonist CGP 42112A significantly increased it in Wistar rats (F1, 34 = 12.553, p = 0.001) (Fig. 1).

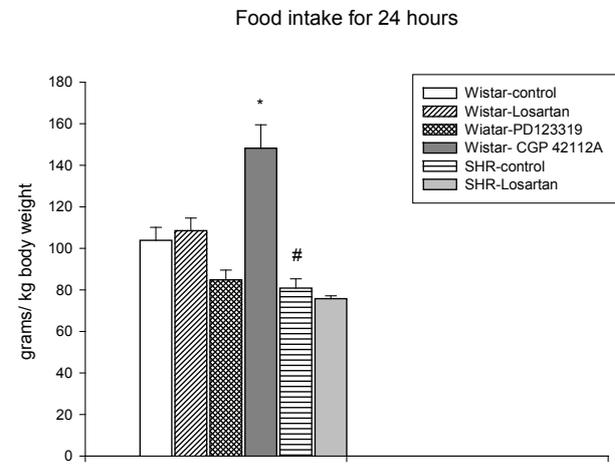
Water intake was similar to food consumption as regards to strain and drug treatment. The SHR control group drank less water compared to Wistar controls (Q = 3.74, p < 0.001). Chronic CGP 42112A treatment significantly increased water intake

(F1, 37 = 10.18, p = 0.003). Moreover, this group showed a strong dipsogenic effect at day 6 after the start of peptide ICV infusion (mean 255.9 ± 47.9 ml/ kg of body weight). Both AT1 and AT2 antagonists did not change the drinking during the period of infusion (Fig. 2).

MEASUREMENT OF URINE AND ELECTROLYTES EXCRETION

Long-term CGP 42112A treatment significantly increased the volume of excreted urine (Q = 3.05, p = 0.002) which corresponded to increased water intake. Neither strain nor receptor antagonists treatment influenced the urine excretion during the period of infusion (Fig. 3).

Fig. 4 shows a decreased UNa+ excretion in SHRs compared to Wistar controls (F1, 35 = 5.024, p = 0.032). Losartan increased UNa+ both



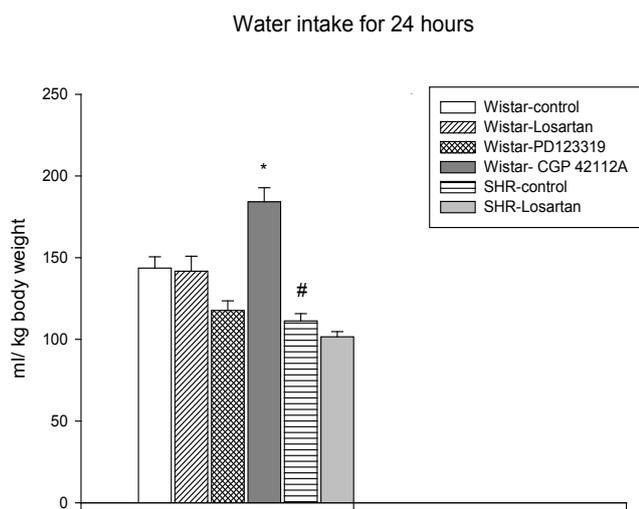
Data are shown as mean ± SEM; *p < 0.05 vs control group; # vs respective Wistar group.

Figure 1. Effects of long-term treatment with AT1 and AT2 receptor blockers losartan and PD123319 and AT2 receptor agonist CGP 42112A on the 24-hour food intake in Wistar rats and SHRs.

Table 1. Body weight (grams)

Strain	Drug - dose (n)	Weight gain after 14 days of treatment
Wistar	Saline 0.5 ml/h (10)	34 ± 3.8
	Losartan 10 mg/kg, IP (7)	35.2 ± 4.2
	PD 123319 10 mg/kg, IP (8)	17.7 ± 1.9 *
	CGP 42112A 12 µg/rat, ICV (9)	14 ± 5.2 *
SHR	Saline 0.5 ml/h (8)	17.2 ± 4.6 #
	Losartan 10 mg/kg, IP (10)	5.5 ± 2.3 *

*p < 0.05 vs control group; # vs respective Wistar group.



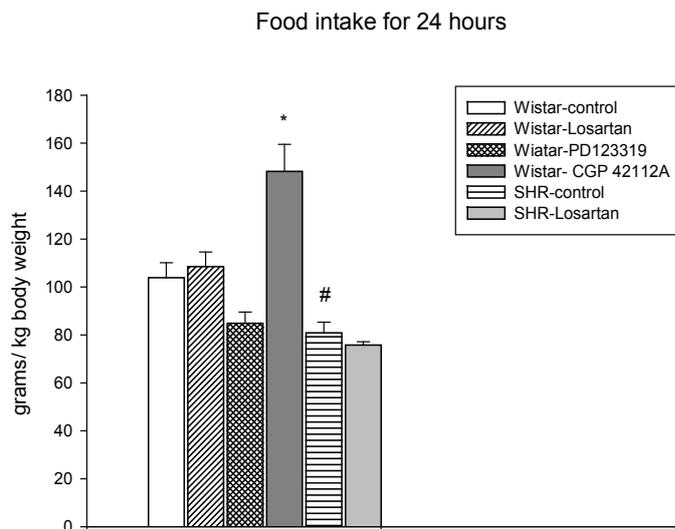
Data are shown as mean \pm SEM; * p < 0.05 vs control group; # vs the respective Wistar group.

Figure 2. Effects of long-term treatment with AT1 and AT2 receptor blockers losartan and PD123319 and AT2 receptor agonist CGP 42112A on the 24-hour water intake in Wistar rats and SHRs.

in Wistar rats ($F_{1, 24} = 6.637$, $p = 0.017$) and in SHRs ($Q = 2.291$, $p = 0.022$). Long-term block of AT2 receptors did not change UNa^+ but chronic CGP42112A infusion increased it about two fold ($F_{1, 27} = 27.854$, $p < 0.001$) in parallel with the increased urine volume. This effect of AT2 agonist was accompanied also by an increase of UK^+ excretion ($Q = 3.812$, $P < 0.001$) (Fig. 5). Both chronic losartan and PD 123319 increased UK^+ in Wistar rats ($F_{1, 24} = 8.565$, $p = 0.008$ and $F_{1, 27} = 7.588$, $P = 0.011$, respectively). SHRs did not differ from Wistar controls as concerns to UK^+ and losartan did not change UK^+ excretion in SHRs (Fig. 5).

DISCUSSION

In the present study we confirmed that SHRs have a lower rate of weight gain compared to normotensive rats¹² accompanied by a decreased food and water intake. Chronic losartan treatment aggravated the decrease in body weight gain of SHRs, as previously reported for another AT1 receptor antagonist candesartan.¹³ In addition, we found that chronic losartan treatment did not change the weight gain in normotensive Wistar rats. Various metabolic effects of ACE inhibitors and AT1 receptor antagonists are described. Chronic AT1 receptor antagonist telmisartan but not losartan, diminishes the increase in body weight in rats fed with high-fat diet.¹⁴ The above mentioned telmisartan-induced attenuation

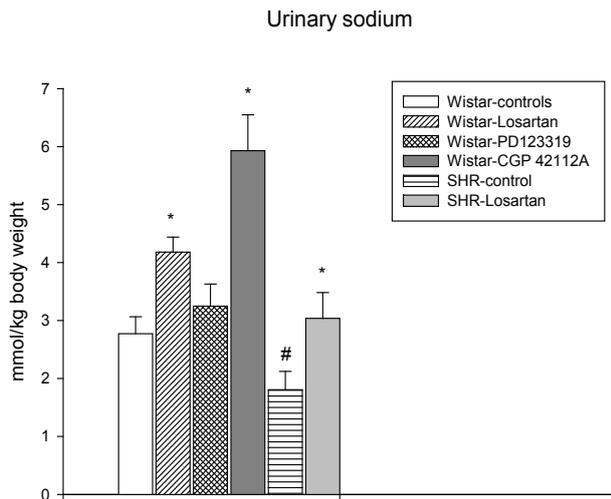


Data are shown as mean \pm SEM; * p < 0.05 vs control group.

Figure 3. Effects of long-term treatment with AT1 and AT2 receptor blockers losartan and PD123319 and AT2 receptor agonist CGP 42112A on the 24-hour urine excretion in Wistar rats and SHRs.

of weight gain could not be attributed to reduced energy intake, because daily food consumption was nearly identical to control and losartan treated groups.

In addition telmisartan augments glucose uptake and GLUT4 expression in adipocytes.¹⁵ A high single dose of irbesartan decreases food and water intake in short-term experiments after food deprivation in normotensive rats.¹⁶ The anorexigenic effect of candesartan is obvious only at a high dose of antagonist and intact leptin signaling and it occurs independently of its ability to lower blood pressure.¹³ These data suggested that AT1 receptor antagonists exerted different effects on weight gain and food intake depending on the chemical structure of the antagonist, animal strain (i.e. normotensive or hypertensive) and the drug dose. The AT2 receptor agonist, however, induced a decrease in weight gain despite a significant increase of food intake. These results are in discrepancy with previously reported data for an anorexigenic activity of AT2 receptor agonist novokinin.¹⁷ Novokinin, however, was injected acutely in fasted mice and its effects on food intake were measured only for 2 hours, while our data showed daily food intake after chronically infused AT2 receptor agonist in rats fed *ad libitum*. The mechanisms mediating this effect of AT2 receptor are not yet elucidated, but brain structures participating in the regulation of feeding like the hypothalamus express this receptor subtype.⁶

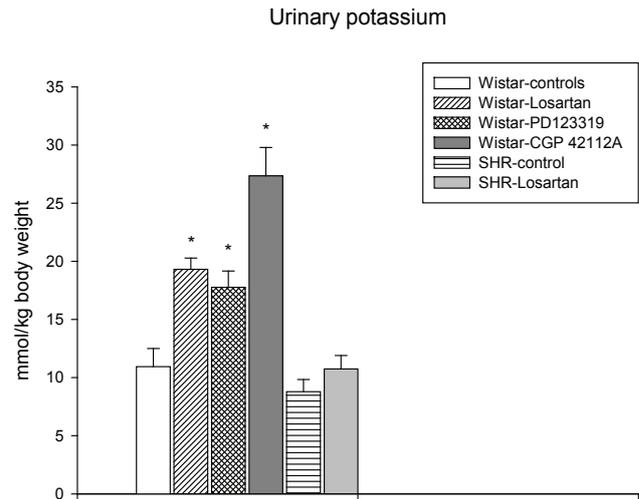


Data are shown as mean \pm SEM; * $p < 0.05$ vs control group; # vs the respective Wistar group.

Figure 4. Effects of long-term treatment with AT1 and AT2 receptor blockers losartan and PD123319 and AT2 receptor agonist CGP 42112A on the 24-hour excretion of Na⁺ in Wistar rats and SHRs.

We found that chronic losartan infusion did not change the volume of water intake and urine excretion, while CGP 42112A produced a significant dipsogenic effect together with increased urine excretion. In earlier studies an acute intracerebroventricular injection of angiotensin II or water deprivation immediately produced increase in water intake and this effect was blocked both by AT1 and AT2 receptor antagonists but not by CGP42112B which have a structure similar to that of the agonist CGP 42112A. These results showed that both brain AT1 and AT2 receptors are involved in dehydration-induced drinking.^{18,19} Under conditions of chronic AT1 receptor block, it is possible that the endogenous Ang II level is not sufficient for the activation of nonblocked AT2 receptors and accomplishment of the dipsogenic effect. Moreover, while the dipsogenic effect elicited by AT1 receptor activation is related to release of vasopressin, AT2 receptors exerted their dipsogenic effect without affecting vasopressin plasma concentration.²⁰ These findings suggest that the regulatory mechanism of water intake mediated by central Ang II differs from that of the pressor response and that AT1 and AT2 receptors in the brain seem to act synergistically in the control of drinking.

In our study the urinary excretion of Na⁺ was lower in SHRs compared to normotensive Wistar rats as already reported.²¹ Losartan increased urinary sodium excretion both in normotensive rats and



Data are shown as mean \pm SEM; * $p < 0.05$ vs control group.

Figure 5. Effects of long-term treatment with AT1 and AT2 receptor blockers losartan and PD123319 and AT2 receptor agonist CGP 42112A on the 24-hour excretion of K⁺ in Wistar rats and SHRs.

SHRs without affecting significantly water intake and urine volume, while CGP increased excreted sodium in parallel with increased urinary volume. Recently it was found that AT1 receptor activation-induced stimulation of sodium appetite has a specific downstream mechanism different from that stimulated by thirst and neurohypophyseal hormone secretion²² suggesting a dichotomy of the effects mediated by AT1 receptor. On the contrary, AT2 receptor activation in proximal tubules decreases sodium reabsorption through an inhibition of Na-K-ATPase activity which might be a mechanism of CGP-induced natriuresis-diuresis.²³ This opposite action of two receptor types on the sodium reabsorption led us to expect that PD123319 will decrease Na⁺ excretion, but this was not confirmed by our data. We had assumed that long-term receptor blockade may result in receptor adaptation as was reported previously.²⁴ Blocking of both AT1 and AT2 receptors enhanced excretion of UK⁺ suggesting a participation of two receptors in the regulation of renal K⁺ reabsorption probably in the proximal tubule and the loop of Henle and/or H⁺/K⁺ exchanges in collecting tubules.²⁵ Increased UK⁺ was established only in normotensive Wistar rats not in SHRs. This finding suggests that Ang II receptors participate in the physiological regulation of the K⁺ turnover which might be disturbed in SHRs. Although Ang II acting on the AT1 receptors stimulates aldosterone release and further causes

sodium reabsorption and potassium secretion in the initial and cortical collecting tubule, blocking of AT1 receptors by losartan is able to recover the decreased potassium excretion induced by estrogen deficiency.²⁶ This suggests that activation of AT1 receptors may play a more complex role in the control of mineral balance.

CONCLUSIONS

Long-term activation of AT2 receptors in the brain results in an increase in food and water consumption as well as urine, sodium and potassium excretion in parallel with a decrease in weight gain. Losartan increased UNa⁺ in both rat strains and decreased weight gain only in SHR without affecting food and water consumption. AT1 and AT2 receptors are involved in the control of water-salt balance which should be taken in consideration when evaluating the consequences of pharmacological manipulations of the renin-angiotensin system.

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ЭФФЕКТЫ ХРОНИЧЕСКОГО ПРИЛОЖЕНИЯ АНГИОТЕНЗИН-РЕЦЕПТОРНЫХ ЛИГАНДОВ НА ВОДНО-СОЛЕВОЙ БАЛАНС У КРЫС WISTAR И КРЫС СО СПОНТАННОЙ ГИПЕРТЕНЗИЕЙ

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РЕЗЮМЕ

ВВЕДЕНИЕ: Ренин-ангиотензиновая система играет важную роль в регулировании функции сердечно-сосудистой системы и в поддержании водно-солевого баланса. Ее два основных типа рецепторов AT1 и AT2 имеют различные, часто противоположные эффекты на эти функции.

Цель: Выяснить влияние продолжительного воздействия селективными ангиотензиновыми рецепторами на водно-солевой баланс у нормотензивных Wistar и спонтанно гипертензивных крыс (SHRs).

МАТЕРИАЛ И МЕТОДЫ: Мужские крысы породы Wistar и SHRs в возрасте 12 нед. распределены индивидуально в метаболические клетки. Отсчитаны количества потребленной пищи и воды, выделенной

мочи и электролитов за 24 ч. Количество натрия (UNa) и калия (UK) в моче определены пламенной фотометрией.

Селективный AT1 рецепторный антагонист лосартан применен в дозе 10 мг/кг в день подкожно у крыс Wistar и SHRs. AT2 рецепторный антагонист PD123319 применен в дозе 10 мг/кг в день подкожно у крыс породы Wistar. AT2 рецепторный CGP 42112A применен в дозе 12 мг/кг в день интрацеребровентрикулярно у крыс породы Wistar.

Все вещества инфузирваны в течение 14 дней посредством осмотических минипомп.

РЕЗУЛЬТАТЫ: Лосартан повысил селективно экскрецию натрия и у двух пород и снизил вес SHRs. PD123319 повысил экскрецию калия и снизил вес крыс породы Wistar. CGP 42112A повысил прием пищи и воды, экскрецию мочи, натрия и калия и снизил вес нормотензивных крыс Wistar.

ЗАКЛЮЧЕНИЕ: Продолжительное воздействие селективными ангиотензиновыми рецепторными лигандами модулирует водно-солевой баланс у крыс посредством изменений в выделительной функции почек и в поведении питания и принятия воды.