Effect of a Calcium Antagonist on Renal Hemodynamics in Salt-loaded Spontaneously Hypertensive Rats

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SUMMARY

In the present study, we investigated the change in renal hemodynamics induced by a calcium antagonist in young (6 week-old) spontaneously hypertensive rats (SHR), a salt-sensitive hypertensive model. In acute experiments, SHR were fed either a 0.66% or 8.0% NaCl diet for 4 weeks. In acute experiments, manidipine, a calcium antagonist, was administered in a bolus dose of 10 μg/kg. In chronic experiments, SHR were fed a 0.66% NaCl, 0.66% NaCl plus 0.05% manidipine, 8.0 % NaCl or 8.0 % NaCl plus 0.05% manidipine diet for 4 weeks. Mean arterial pressure (MAP), glomerular filtration rate (GFR), and renal blood flow (RBF) were measured. Salt loading increased MAP in young SHR. Acute administration of manidipine decreased MAP more in salt-loaded SHR compared to non-salt-loaded SHR (-43.3 ± 3.1 vs. -18.6 ± 2.1 mmHg: $p < 0.01$). Moreover, chronic administration of manidipine attenuated the rise in MAP in salt-loaded SHR (155 ± 3 mmHg vs. 196 ± 5 mmHg: $p < 0.01$) and less so in non-salt-loaded SHR (150 ± 2 mmHg vs. 160 ± 3 mmHg: $p < 0.01$). Salt loading elevated renal vascular resistance (RVR) but changed neither RBF nor GFR. The acute- and chronic-administration of manidipine increased RBF (Acute; $+0.77 \pm 0.22$ m*l*/min/g kidney: $p < 0.05$, Chronic; 4.32 ± 0.29 vs. 5.50 ± 0.90 m*l*/min/g kidney: $p < 0.01$) in non-salt-loaded SHR, which was greater in salt-loaded SHR (Acute; $+2.19 \pm 0.52$ m*l*/min/g kidney: $p < 0.05$ vs. non-salt-loaded SHR, Chronic; 4.29 ± 0.53 vs. 6.09 ± 1.41 m*l*/min/g kidney: $p < 0.01$) Manidipine also decreased RVR (Acute; -10.2 ± 2.2 mmHg/m*l*/min/g kidney: $p < 0.01$, Chronic; 35.3 ± 1.6 vs. 27.3 ± 4.1 mmHg/m*l*/min/g kidney: $p < 0.01$) in non-salt-loaded SHR, which was greater in salt-loaded SHR (Acute; -21.1 ± 3.1 mmHg/m*l*/min/g kidney: $p < 0.01$ vs. non-salt-loaded SHR, Chronic; 44.9 ± 2.6 vs. 27.6 ± 4.1 mmHg/m*l*/min/g kidney: $p < 0.01$). GFR did not change significantly following manidipine. It is suggested that the antihypertensive effect of the calcium antagonist, manidipine, was greater in salt-loaded SHR and was accompanied by profound amelioration of the abnormal renal hemodynamics. (Jpn Heart J **36**: 797–805, 1995)

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VARIOUS calcium antagonists such as nifedipine or nitrendipine are being successfully used in the treatment of systemic hypertension. Calcium antagonists are particularly effective in salt hypertension[1,2] but their mechanism of action is not clear. Several calcium antagonists have been studied for short- and long-term effects on renal blood flow (RBF), glomerular filtration rate (GFR) and sodium excretion; calcium antagonists maintain or increase the GFR and reduce renal vascular resistance (RVR).[3,4] The ability of calcium antagonists to increase RBF and GFR was reported to be determined by the preexisting vascular tone.[3,4] Thus, calcium antagonists may be effective in treating salt-sensitive hypertensives because previous studies suggest that the salt-induced rise of blood pressure (BP) may be partly attributed to an abnormality of renal sodium handling[5-7]; the abnormal renal hemodynamics and resultant impaired renal function in sodium excretion are common characteristics of salt-sensitive hypertensive patients[2,8] and animals.[9,10]

Thus, we designed the present study to clarify the effect of a calcium antagonist manidipine[11] on both BP and renal hemodynamics in salt-loaded young (6-week-old) spontaneously hypertensive rats (SHR), a salt-sensitive hypertensive model.[10]

Methods

Animal preparation: Fifty-eight male SHR were purchased from Charles River Japan (Atsugi, Japan) at 5 weeks of age. All rats were housed in a quiet room with constant temperature (24 ± 1°C), humidity (60 ± 5%), and light (illumination from 6 a.m. to 6 p.m.).

Protocol 1; Acute effect of manidipine. Five days after arrival, eighteen rats were randomly divided into two groups as follows (9 rats for each group): the non-salt-loaded group was placed on a 0.66% NaCl diet (Oriental Yeast Co., Tokyo); the salt-loaded group was placed on an 8.0% NaCl diet.

Protocol 2; Chronic effect of manidipine. Five days after arrival, forty rats were randomly divided into four groups as follows (10 rats for each group): the non-salt-loaded group was placed on a 0.66% NaCl diet; the salt-loaded group was placed on an 8.0% NaCl diet; the non-salt-loaded manidipine-treated group was placed on a 0.66% NaCl plus 0.05% manidipine diet; and the salt-loaded manidipine-treated group was placed on an 8.0% NaCl plus 0.05% manidipine diet.

These 6 groups of rats each received diet and tap water ad libitum for 4 weeks. Body weight was determined on the same day as the experiment.

Measurements of Renal Hemodynamics: Ten week-old rats were anesthetized with ether, and the left carotid artery and jugular vein were cannulated with tip-tapered PE-50 polyethylene tubing. The venous and arterial catheters were

tunneled to the back of the neck, filled with heparinized saline (200 U/m*l*), and plugged with stainless steel pins. The bladder was exposed through a suprapubic incision and was connected with PE-60 tubing that was flared at one end. The flared end was advanced to cover the trigone and ligated to minimize dead space while allowing urine to flow freely. The incision was closed by sutures. After the rats were placed in a Lucite restraining chamber that permitted forward and backward movement for at least three hours to eliminate the effect of ether, isotonic saline containing 1 mg/m*l* inulin and 1 mg/m*l* p-aminohippuric acid (PAH) was infused at a rate of 1.48 m*l*/h for one hour through the venous catheter. Throughout the clearance study, carotid arterial pressure was measured as mean arterial pressure (MAP) by use of a pressure transducer (model TP-200T; Nihon Kohden, Tokyo, Japan) connected to a thermal array recorder (model WS-641G; Nihon Kohden).

In protocol 1 (acute experiment), urine was collected for three continuous 20 minute periods before and 30 minutes after administration of manidipine (Takeda Chemical Industries, Osaka, Japan) in a dose of 10 mg/kg by bolus injection. Venous samples (200 μl) were taken at the midpoint of each clearance period and at the end of the experiment.

In protocol 2 (chronic experiment), urine was collected for two 20 minute periods and venous samples (200 μl) were taken at the midpoint of each clearance period and at the end of the experiment.

Urine volume was determined gravimetrically. Hematocrit was measured in heparinized capillary tubes. Glomerular filtration rate (GFR) was measured as inulin clearance. Effective renal plasma flow (ERPF) was determined by PAH clearance. Urine and plasma inulin and PAH concentrations were determined by anthrone[12] and ethylenediamine methods,[13] respectively. Measured values were not corrected for the extraction of PAH. Filtration fraction (FF) was calculated as the ratio of GFR/ERPF. Renal blood flow (RBF) and renal vascular resistance (RVR) were calculated as ERPF/(1-hematocrit) and MAP/RBF, respectively. The average MAP during urine collection was used for calculation of renal hemodynamics. The concentration of manidipine at the end of the experiment was also measured using thin layer chromatography as described elsewhere.[14]

Statistical analysis: Data are presented as means ± SE. Statistical analyses were performed using unpaired and paired Student's t-test, repeated measurements, or two-way analysis of variance (ANOVA) and subsequently Tukey's method. A p value less than 5% was considered significant.

Results

Protocol 1; Acute administration of manidipine

Effect on blood pressure: Basal characteristics of the two groups were not significantly different (Table I). As shown in Figure 1, high salt diet significantly elevated MAP in young SHR (196 ± 3 versus 159 ± 1 mmHg; $p < 0.01$). Manidipine at a dose of 10 mg/kg decreased MAP significantly both in salt-loaded and non-salt-loaded SHR 10 minutes after administration. MAP was stable from 20 minutes through 60 minutes after administration (Figure 1). Manidipine treatment decreased MAP significantly more in salt-loaded SHR (30 minutes after: 43.3 ± 3.1 versus −18.6 ± 2.1 mmHg; $p < 0.01$), although serum concentration of manidipine after the experiment did not differ between groups (Table I).

Effect on GFR, RBF, and RVR: Salt loading did not alter RBF or GFR despite increased RVR (Table II). Manidipine treatment did not change GFR in either group. RBF was increased both in salt-loaded and non-salt-loaded SHR by

Table I. Basic Characteristics of Rats Receiving Acute Administration of Manidipine

	BW (g)	Ht (%)	TP (mg/dl)	MH (ng/ml)
SHR	255.3 ± 2.2	51.4 ± 0.1	5.1 ± 0.1	2.44 ± 0.28
SHR-Na	250.7 ± 3.0	50.2 ± 0.0	5.2 ± 0.1	2.28 ± 0.24

Data are presented as means ± SE. Data not statistically different between two groups using Student's unpaired t-test. SHR = non-salt-loaded SHR; SHR-Na = salt-loaded SHR; Ht = Hematocrit; TP = serum total protein;, MH = serum concentration of manidipine.

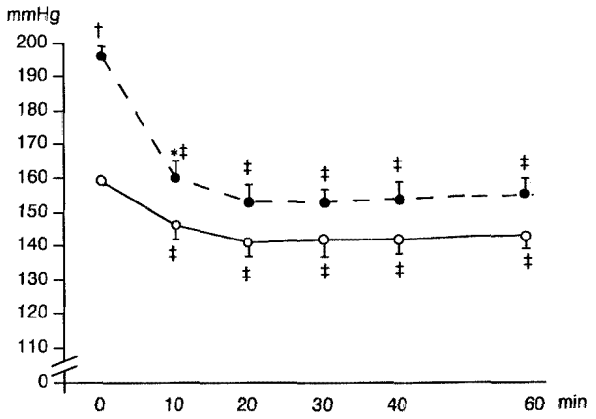

Figure. Mean arterial pressure changes with acute administration of manidipine. Solid line for non-salt-loaded SHR and dotted line for salt-loaded SHR. Note that a bolus injection of manidipine at a dose of 10 mg/kg decreased mean arterial pressure (MAP) significantly both in salt-loaded and non-salt-loaded SHR 10 minutes after administration. The decrease in MAP stabilized 20 minutes after administration. * $p < 0.05$ versus non-salt-loaded SHR, † $p < 0.01$ versus non-salt-loaded SHR by Student's unpaired t-test. ‡ $p < 0.01$ versus before manidipine by repeated measurement of ANOVA.

Table II. Changes in Renal Hemodynamic Parameters with Acute Administration of Manidipine

	GFR (ml/min/g kidney)		RBF (ml/min/g kidney)		RVR (mmHg/ml/min/g kidney)	
	before	after	before	after	before	after
SHR	0.63 ± 0.04	0.66 ± 0.05	4.33 ± 0.31	5.10 ± 0.47‡	37.4 ± 7.0	27.2 ± 6.1§
Difference	0.02 ± 0.05		0.77 ± 0.22		−10.2 ± 2.2	
SHR-Na	0.66 ± 0.06	0.68 ± 0.07	4.29 ± 0.43	6.51 ± 0.51§	45.3 ± 5.9†	24.2 ± 3.3§
Difference	0.03 ± 0.07		2.19 ± 0.52*		−21.1 ± 3.1†	

Data are presented as means ± SE. * $p < 0.05$ versus non-salt-loaded SHR, † $p < 0.01$ versus non-salt-loaded SHR by Student's unpaired t-test. ‡ $p < 0.05$ versus before manidipine, § $p < 0.01$ versus before manidipine by Student's paired t-test. SHR = non-salt-loaded SHR; SHR-Na = salt-loaded SHR; RBF = renal blood flow; RVR = renal vascular resistance; before = before manidipine administration; after = after administration of manidipine at a dose of 10 mg/kg in bolus; Difference = the difference of values between before and after manidipine treatment.

Table III. Basic Characteristics of Rats Receiving Chronic Treatment with Manidipine

	BW (g)	MAP (mmHg)	Ht (%)	TP (mg/dl)	CV (ng/ml)
SHR	250.8 ± 2.8	160 ± 3	50.5 ± 2.9	5.1 ± 0.1	—
SHR-Na	242.1 ± 3.3	196 ± 5*	50.8 ± 3.1	5.2 ± 0.1	—
SHR-M	239.3 ± 4	150 ± 2*	51.5 ± 3.3	5.2 ± 0.1	12.43 ± 2.2
SHR-Na-M	220.3 ± 6	155 ± 3†	50.4 ± 2.8	5.4 ± 0.1	11.57 ± 1.3

Data are presented as means ± SE. * $p < 0.01$ versus non-salt-loaded SHR, † $p < 0.01$ versus salt-loaded SHR by ANOVA and subsequent Tukey's method. SHR = non-salt-loaded SHR; SHR-Na = salt-loaded SHR; SHR-M = non-salt-loaded manidipine-treated SHR; SHR-Na-M = salt-loaded manidipine-treated SHR; BW = Body weight; MAP = Mean arterial pressure; Ht = Hematocrit; TP = serum total protein; CV = serum concentration of metabolites of manidipine.

Table IV. Renal Hemodynamic Parameters after Chronic Treatment with Manidipine

	GFR (ml/min/g kidney)	RBF (ml/min/g kidney)	RVR (mmHg/ml/min/g kidney)	FF (%)
SHR	0.63 ± 0.05	4.32 ± 0.29	35.3 ± 1.6	28.6 ± 3.8
SHR-Na	0.66 ± 0.08	4.29 ± 0.53	44.9 ± 2.6*	30.3 ± 4.0
SHR-M	0.64 ± 0.09	5.50 ± 0.90*	27.3 ± 4.1*	24.3 ± 5.5
SHR-Na-M	0.68 ± 0.10	6.09 ± 1.41†	27.6 ± 4.1†	23.5 ± 5.3‡

Data are presented as means ± SE. * $p < 0.01$ versus non-salt-loaded SHR, † $p < 0.01$ versus salt-loaded SHR, ‡ $p < 0.05$ versus salt-loaded SHR by ANOVA and subsequent Tukey's method. SHR = non-salt-loaded SHR; SHR-Na = salt-loaded SHR; SHR-M = non-salt-loaded-manidipine SHR; SHR-Na-M = salt-loaded-manidipine SHR; RBF = renal blood flow; RVR = renal vascular resistance; FF = filtration fraction.

manidipine, but the change in RBF was significantly greater ($p < 0.05$) in salt-loaded SHR. RVR decreased significantly in both groups. The decrement of RVR was also greater in salt-loaded SHR ($p < 0.01$). FF decreased in salt-loaded groups (from 30.5 ± 3.2% to 21.9 ± 4.1%; $p < 0.05$) but not in non-salt-loaded SHR (from 28.8 ± 4.5% to 25.4 ± 3.9%; n.s.).

Protocol 2; Chronic administration of manidipine

Effect on blood pressure: As in protocol 1, high salt diet significantly elevated MAP

in young SHR (Table III). Chronic treatment with manidipine attenuated the rise of MAP profoundly in salt-loaded SHR and slightly in non-salt-loaded SHR. As a result, MAP was similar between manidipine- and manidipine plus salt-treated rats. The concentrations of metabolites of manidipine were not significantly different between the two groups. Other basal characteristics of the four groups did not differ significantly.

Effect on GFR, RBF, and RVR: Renal hemodynamics were studied twice and the mean value was calculated for each rat. As shown in Table IV, chronic treatment with manidipine did not change GFR. RBF increased and RVR decreased significantly following manidipine treatment in both salt-loaded and non-salt loaded SHR. Although RVR was elevated in salt-loaded SHR compared with non-salt-loaded SHR without manidipine, RVR did not differ between manidipine-treated groups. FF was lower in salt-loaded manidipine-treated SHR compared to salt-loaded SHR, but manidipine did not significantly affect filtration fraction in non-salt-loaded SHR.

Discussion

Both acute and chronic administration of manidipine[11] showed a greater depressor effect accompanied by renal vasodilatation in salt-loaded SHR. Thus, manidipine decreased blood pressure more effectively in salt hypertension, probably due to amelioration of abnormal renal hemodynamics.

It has been reported that salt-sensitivity is closely linked to renal hemodynamics.[5–7] Salt-sensitive hypertensive patients and an animal model showed increased renal vascular resistance (RVR) with salt loading.[8,10] In the present study, we also showed that salt-loading elevated renal vascular resistance in SHR as shown in the previous study.[10] Studies with hypertensive models have shown that afferent renal arterial resistance (R_A) was also elevated compared to normotensive models.[15] Increased R_A implies reduced intraglomerular pressure and impaired ability to excrete excess sodium. Thus high R_A may induce volume retention and high blood pressure. In the present data, the salt-induced rise in BP was accompanied by increased RVR but without alteration of GFR, which suggests that R_A was elevated in salt-loaded SHR. In fact, when we calculated intrarenal hemodynamics,[16] R_A increased with salt-loading in SHR (35.2 ± 4.3 unit vs. 26.9 ± 3.5 unit; $p < 0.01$) (The calculation applied here was performed with several assumptions and thus it requires confirmation by other more direct methods such as micropuncture.). On the other hand, efferent renal arterial resistance (R_E) was reported to be elevated in salt hypertension.[2] R_E calculated by the present data was increased by salt-loading in young SHR (13.8 ± 2.8 units vs. 9.2 ± 2.7 units; $p < 0.05$); increased R_E may increase glomerular pressure to facilitate renal so-

dium excretion.

In the present study, manidipine reduced blood pressure to a greater degree in salt-loaded SHR than non-salt-loaded SHR. Moreover, the reduction of RVR or increment of RBF was greater in salt-loaded SHR. Our results are also consistent with previous reports: dihydropyridine derivatives are effective in treating hypertension, partly due to changing renal hemodynamics. They are reported to be more effective in salt-loaded hypertensive patients.[1,2] RVR and RBF are determined by afferent and efferent renal arterial resistance. As mentioned above, the changes in RA and RE following manidipine were also calculated by Gomez's method.[16] The decrease in RA was greater in salt-loaded SHR (-15.60 ± 2.32 versus -7.67 ± 1.28 unit; $p < 0.01$). RE decreased significantly with manidipine in salt-loaded SHR (-4.04 ± 1.24 unit) but not in non-salt-loaded SHR (-1.50 ± 0.98 unit). The decrease in RE was also significantly greater in salt-loaded SHR. As a result, RA and RE did not differ between salt-loaded and non-salt-loaded SHR after manidipine treatment. The same tendency was observed in chronic experiments (data not shown). These data suggest for the first time that the effectiveness of manidipine in salt-loaded salt sensitive hypertensives results from cancelation of salt-induced intrarenal hemodynamic changes.

Renal afferent vasoconstriction may protect the glomeruli from the adverse effects of hypertension through attenuation of intraglomerular hypertension.[15,17] Thus, changes in RA may have both disadvantages (count for blood pressure elevation) and advantages. Thus, increases in RA (sodium retention and glomerular protection) and RE (sodium excretion and glomerular damage) may exert opposite effects on kidney protection in salt-loaded SHR. Calcium antagonists have been demonstrated to decrease RA but not RE in non-salt-loaded models.[18] Thus, there is a possibility that calcium antagonists might have a disadvantage in inducing glomerular damage by enhancing glomerular hypertension although they have a greater antihypertensive effect in salt hypertension. However, this may not be so in the case of manidipine. In the present study, FF decreased with manidipine in salt-loaded SHR but not in non-salt-loaded SHR, which suggests that manidipine decreased RE and in fact as mentioned above, RE decreased only in salt-loaded SHR. In patients with salt-sensitive hypertension with salt-loading, nifedipine has also been reported to decrease RE.[2]

The reduced RE might be effective in reducing intraglomerular pressure (PG). In rats after extensive ablation of renal mass,[19] it was suggested that increases in capillary pressure and plasma flow rate may directly damage the glomerulus. Also, reversal of increased PG, by reducing protein intake or treatment with angiotensin converting enzyme inhibitor, resulted in improvement of the glomerular injury without decreasing systemic blood pressure in experimental kidney disease.[20,21] Moreover, in hypertensive models such as SHR or

deoxycorticosterone-salt hypertensive rats, an augmented PG overt renal structural damage[22-24] and reduction of PG protected against the renal morphologic abnormalities.[22,23] Thus, in antihypertensive treatment, effects on intrarenal hemodynamic changes may be important in regard to protecting the kidneys from hypertensive complications. In addition, manidipine exerted not only a more potent depressor effect in salt-loaded hypertension, but also may be beneficial with respect to renal protection.

In conclusion, salt loading increased BP and renal vascular resistance, RA and RE in young SHR. The calcium antagonist, manidipine, showed a more potent depressor effect in salt-loaded SHR. Moreover, the effect of manidipine on renal hemodynamics might be beneficial in protecting the kidney from hypertensive damage.

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