Journal of Human Hypertension (1998) 12, 355–362

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ORIGINAL ARTICLE

Mild exercise activates renal dopamine system in mild hypertensives

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***Objective*: The role of renal dopamine in the early depressor effect of exercise was evaluated in hypertensives.**

***Methods*: After a general clinical observation period of 4 weeks, 29 essential hypertensives were divided into two groups. The exercise group (n = 16) underwent blood lactate threshold exercise using a cycle ergometer for 60 min three times a week for 4 weeks.**

***Results*: In the non-exercise group (n = 13), blood pressure (BP) and humoral variables did not change significantly (from 150 ± 3/93 ± 2 to 145 ± 2/94 ± 1 mm Hg). In the exercise group (n = 16), resting BP was significantly reduced from 158 ± 2/92 ± 2 at week 0 to 145 ± 3/85 ± 3 mm Hg at week 4. The increase in urinary free dopamine excretion (from 248 ± 14 to 276 ± 24 ng/mg Cr) at week 4 was significantly higher than that in the non-exercise group (from 220 ± 31 to 196 ± 27 ng/mg Cr). In the exercise group, urinary kallikrein activity also increased significantly from 173.0 ± 35.4 at week 0 to 320.3 ± 63.3 ng bradykinin/min/mg Cr at week 4. These changes in urinary free dopamine excretion and urinary kallikrein activity were negatively correlated with the change in BP. The change in urinary sodium excretion was also negatively correlated with the change in plasma volume index. Moreover, the change in urinary free dopamine excretion was positively correlated with the changes in urinary kallikrein activity and urinary sodium excretion. The change in renal decarboxylation rate of DOPA (3,4-dihydroxyphenylalanine) positively correlated with the changes in urinary free dopamine excretion and urinary sodium excretion, and was negatively correlated with the change in systolic BP.**

***Conclusion*: These results suggest that exercise triggered renal dopamine generation and activation of renal kallikrein-kinin system, resulting in natriuresis and BP reduction in the early phase (4 weeks) of mild exercise.**

Keywords: exercise therapy; blood pressure; essential hypertension; urinary free dopamine; aromatic-L-amino-acid decarboxylase; urinary kallikrein activity

Introduction

Exercise is now widely recommended as one of the lifestyle modifications that can effectively lower blood pressure (BP) in mild-to-moderate essential hypertension.[1,2] However, the precise anti-hypertensive mechanism of exercise is not well understood. We have previously reported a series of studies involving a 10-week mild exercise programme at lactic threshold intensity (approximately 40–60% maximum O2 consumption) using a cycle ergometer. In these studies, the BP always significantly reduced in the exercise group only. Exercise training appears to modify multiple factors that may participate in maintaining elevated BP.[3,4] The anti-hypertensive effect of exercise involves two mechanisms: first, a reduction in sympathetic nerve activity, as reflected in reduced plasma noradrenaline levels;[5–11] and second, plasma volume depletion, which was substantiated by increases in plasma prostaglandin E,[5] serum taurine,[12] and urinary total dopamine excretion (U-t-DA)[13] and decreases in both the plasma level of endogenous ouabain-like substance and the erythrocyte mean corpuscular volume.[14] In particular, an increase in urinary total (free + conjugated) dopamine (DA) occurs during the early phase of exercise (at week 4) when atrial natriuretic peptide (ANP) levels drop significantly.[13] The renal DA system is one of the renal depressor mechanisms, together with the renal kallikrein-kinin system and the prostaglandin system, and is generally suppressed in essential hypertensives. Our previous study showed that the change in urinary kallikrein activity (U-Kal) in the exercise group was significantly greater than that of the non-exercise group at week 1 and week 2.[15] Iimura *et al*[16] found that urinary free DA output is especially low in low-renin essential hypertensives, and that this was due to reduced renal conversion of plasma DOPA (3,4-dihydroxyphenylalanine) to DA.[17–19] Since 70% of urinary DA exist as the inactivated conjugated form,[20] we investigated free DA excretion (U-f-DA) rather than U-t-DA and the mechanism of the increase of renal DA.

The aim of this study was to determine how the renal DA system is activated and contributes to lowering BP during the first 4 weeks of mild exercise in hypertensives.

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Received 29 September 1997; revised 16 January 1998; accepted 3 February 1998

Subjects and methods

Subjects

Twenty-nine Japanese patients (5 male, 24 female) aged 39–64 years (mean ± s.e.m., 51.6 ± 2.0) with essential hypertension (BP ⩾140/90 mm Hg) were included in the study. Informed consent was obtained from all subjects. After a general clinical observation period of 4 weeks without any medication, subjects were randomly assigned to exercise (*n* = 16; 3 male, 13 female) or non-exercise (n = 13; 2 male, 11 female) group. Eight out of 13 females in the exercise group and seven out of 11 females in the non-exercise group were post menopausal and no patient was taking oral contraceptives. Comparing the two groups, there were no differences in age, body weight, systolic BP (SBP), diastolic BP (DBP), or heart rate at week 0. All subjects had mild hypertension (150 ± 3/93 ± 2 mm Hg) without severe obesity (average body mass index, 24.6 ± 0.5 kg/m^2). Their serum creatinine concentrations were <1.2 mg/dl (mean ± s.e.m., 0.64 ± 0.03). Careful physical and laboratory examinations were performed to rule out secondary hypertension and serious cardiovascular and cerebrovascular complications. We also performed echocardiography in all subjects using an SSD-870 (Aloca Inc, Tokyo, Japan) with a 3.75-MHz transducer by a skilled cardiologist in our department. No subjects had left ventricular hypertrophy. All subjects were instructed to maintain their usual lifestyles, and were periodically monitored by measuring body weight and by a questionnaire concerning their daily activities.

BP and heart rate measurements

Resting BP and heart rate were measured indirectly at the left arm with the patient in the sitting position after 5 min rest by an automatic BP recorder (model 230i, Nihon Colin, Japan), and the mean value of duplicate measurements was recorded. Measurements were obtained once a week during the 4-week observation period. The mean values obtained at the last two visits of each week during exercise therapy were used.

Method of exercise

In order to determine the lactate threshold, all subjects performed a test of multistage graded submaximal exercise on an electric cycle ergometer at weeks 0 and 4 (Lode's Instrumentation BV, Groningen, Netherlands) as described previously.[5,6] The work rate at the blood lactate threshold level (approximately 40–60% of maximum oxygen consumption) was thus individually determined. Using this individual lactate threshold intensity, exercise was performed in an air conditioned laboratory three times a week for 4 weeks.

Haemodynamic variables

In the exercise group, cardiac output and plasma volume were determined after a 12-h fast.[6] Cardiac output at rest was measured at weeks 0 and 4 using a dye-dilution technique with indocyanine green as the indicator and with an earpiece detector (models MLC-4100M and JO-410V, Nihon Kohden Co, Ltd, Tokyo, Japan).[21] Three consecutive determinations were made and the average value was obtained. The coefficient of variation calculated in 107 hypertensive subjects in our laboratory was 5.4%.[6] Total peripheral resistance was calculated from the cardiac output and the mean BP. Plasma volume was determined using the [^{131}I]-labelled human serum albumin method described by Crispel *et al*[22] at weeks 0 and 4. These values were divided by body surface area (the Dubois method) and expressed as an index.

Humoral variables and electrolytes

Twenty-four hour urine and 12-h fasting blood samples were collected 2 days after the last exercise at weeks 0, 1, 2, and 4 in both groups. Twenty-four hour supervised ice-cooled urine sampling was performed using a portable device[23] as previously reported from our laboratory.[15] Blood samples were obtained via a catheter placed in an antecubital vein after the subject had rested in a quiet room for 10 min in the sitting position. Samples were immediately placed on ice and centrifuged at 3000 rpm at 4°C. All samples were stored at −70°C until analysis.

Plasma renin activity (PRA) (radioimmunoassay), aldosterone (radioimmunoassay) concentrations and serum creatinine, sodium, and potassium concentrations were measured. Urinary catecholamines (see below), kallikrein,[15] aldosterone (radioimmunoassay), sodium, potassium (Ion selective electrode) and creatinine, and intrinsic creatinine clearance (Ccr) were measured. All urinary variables were corrected for urinary creatinine concentration to minimise errors of 24-h urine collection.

Assay of catecholamines

Plasma free catecholamines (CAs) in both groups and total (free + sulfoconjugated) CAs in the exercise group were measured at weeks 0, 1, 2, and 4. Blood samples (14 ml) were obtained in the sitting position and transferred to an ice-chilled centrifuge tube containing 10 mg EDTA-2Na. After the blood was mixed by gentle inversion, the plasma was separated from the blood cells by centrifugation (11 750 g) at 4°C for 10 min and stored at −70°C until assayed. Plasma samples (1200 μL) were incubated with arylsulfatase (AS) (152 mU) (Sigma, Type VI) in 0.01 mol/L Tris buffer (pH 7.6) in a total volume of 1300 μL at 37°C for 30 min. The reaction was stopped by the addition of 600 μL of a mixed solution of 0.35 mol/L sodium acetate and 6% perchloric acid. After centrifugation (11 750 g) for 20 min at 4°C, the supernatant was placed in the HPLC analyser (TSK gel CatecholPak, Tosoh Co, Tokyo, Japan).[24] Sulfoconjugated CAs were obtained by subtracting free CAs from total CAs. We used a pH of 7.6 for AS deconjugation, which we have found to be optimal,[25] rather than pH 8.3, which was used in previous studies.[24,26]

Urinary CAs were measured at weeks 0, 1, 2, and 4 in both groups. Urinary total CAs were also measured by HPLC after urine samples were hydrolised with EDTA-2Na and a 4N HCl for 25 min.

Statistical analysis

All values are expressed as means ± s.e.m. All statistical tests were performed using the Statistical Analysis System (SAS Institute, Inc, Cary, NC, USA). The significance of differences in measured values was evaluated by analysis of variance and subsequent Scheffe test for *post hoc* analysis. Simple correlation coefficients were calculated by simple regression analysis between all variables. Stepwise multiple regression analysis was used to examine the relative importance of each biochemical variable in relation to changes in BP or humoral variables. A value of $P < 0.05$ was considered statistically significant.

Results

Changes in SBP, DBP, heart rate, body weight and fitness capacity

In the exercise group, resting BP decreased significantly after exercise for 4 weeks (both SBP and DBP, $P < 0.01$) (Table 1, Figure 1), with no change in body weight (Table 1). This reduction was only seen in the exercise group, without reduction seen in the non-exercise control group. Moreover, the time-course of changes in mean BP (MBP) and DBP in the two groups differed significantly ($P < 0.01$; Figure 1). Body weight and heart rate did not change significantly in either group (Table 1). The work rate at the lactate threshold (WLT) in the exercise group increased significantly ($P < 0.05$; Table 1).

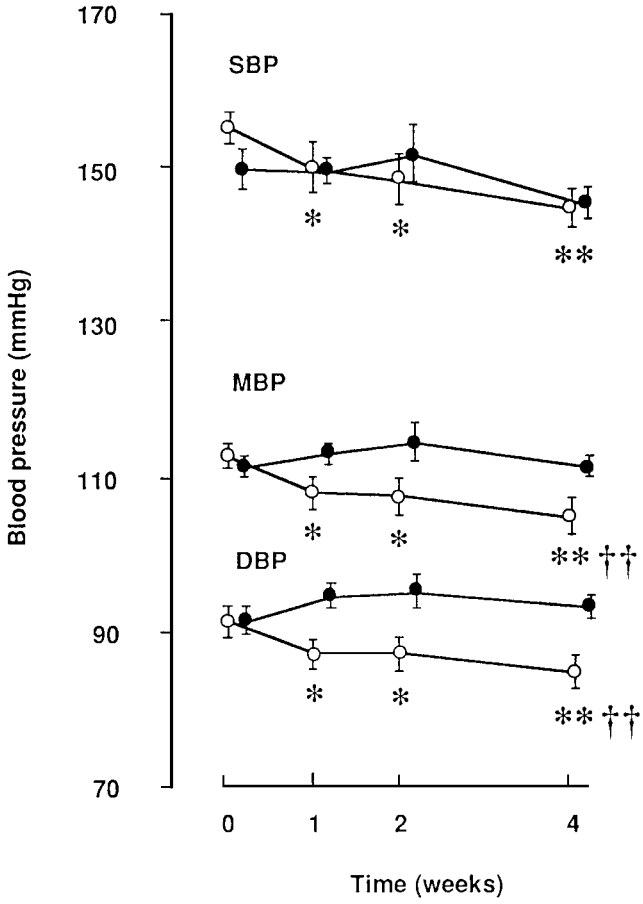

Figure 1 Changes in BP between the exercise (○) and non-exercise (●) groups. SBP, systolic blood pressure, MBP, mean blood pressure; DBP, diastolic blood pressure. Values are expressed as mean ± s.e.m. *$P < 0.05$, **$P < 0.01$ *vs* week 0; ††$P < 0.01$ *vs* non-exercise group. Values of non-exercise group at week 1, 2 and 3 were not different from the value at week 0.

Changes in haemodynamics and plasma and urinary variables

In the exercise group, the cardiac index was significantly reduced. There were no significant differences in the plasma volume index (PVI) or total peripheral resistance index (Table 2).

In both groups, PRA, plasma CAs concentrations, and U-t-DA, U-f-NA, U-t-NA, urinary potassium excretion and urinary sodium excretion (U-Na) remained unchanged (Table 3). Plasma aldosterone, U-f-Ad, U-t-Ad, serum sodium and potassium concentrations, urinary potassium excretion, urine volume, and Ccr also remained unchanged (data not shown). The ratio of serum sodium to potassium (Na/K) did not change significantly in either group.

There were no differences in baseline U-Kal, U-f-DA, and U-t-DA between the two groups. In the

Table 1 Characteristics of subjects

	Exercise group (n = 16)		*Non-exercise group (n = 13)*	
	Week 0	*Week 4*	*Week 0*	*Week 4*
Number (M:F)	16(3:13)	—	13(2:11)	—
Age (years)	56 ± 2	—	52 ± 2	—
Height (cm)	158 ± 2	—	156 ± 2	—
Weight (kg)	61.3 ± 2	61.0 ± 2	59.3 ± 2	61.0 ± 2
SBP (mm Hg)	156 ± 2	145 ± 3**	150 ± 3	145 ± 2
DBP (mm Hg)	92 ± 2	85 ± 3**†	93 ± 2	94 ± 1
Heart rate (beats/min)	74 ± 2	74 ± 3	75 ± 2	76 ± 2
WLT (W)	32.5 ± 5.0	43.6 ± 3.6*	—	—

Values are expressed as mean ± s.e.m.
*$P < 0.05$, **$P < 0.01$ *vs* week 0; †$P < 0.01$ *vs* non-exercise group.
SBP, systolic blood pressure; DBP, diastolic blood pressure; WLT, workload at the lactate threshold.

Table 2 Changes in haemodynamic variables in the exercise group

Variables	*Week 0*	*Week 4*
Heart rate (beats/min)	74 ± 2	74 ± 3
SV (mL/beat)	60.7 ± 3.4	55.5 ± 3.7
CI (L/min/m^2)	2.55 ± 0.15	2.21 ± 0.30*
TPRI (mm Hg/L/m^2/min)	29.8 ± 2.0	33.8 ± 2.2
PVI (mL/m^2)	1662 ± 41	1659 ± 40

Values are expressed as mean ± s.e.m. *$P < 0.05$ *vs* week 0. SV, stroke volume; CI, cardiac index; TPRI, total peripheral resistance index; PVI, plasma volume index.

exercise group, U-Kal increased significantly after 4 weeks ($P < 0.01$; Table 3). U-f-DA showed a tendency to increase in the exercise group ($P = 0.07$; Figure 2), but U-f-DA and U-t-DA at week 4 were significantly higher than in the non-exercise group ($P < 0.05$; Table 3). The changes in U-f-DA from week 0 to week 4 in the exercise group tended to be greater than in the exercise group ($P = 0.07$). The time-course of changes in U-f-DA and U-t-DA in the two groups differed significantly ($P < 0.05$; Figure 2).

Correlation coefficients between BP and humoral variables

As the changes in U-f-DA in the exercise group tended to be greater than in the non-exercise group, simple correlation coefficients were calculated by simple regression analysis between BP changes and changes in humoral variables over the same period in the exercise group. As shown in Table 4, the change in U-f-DA was negatively correlated with the changes in SBP ($P < 0.01$) and DBP ($P < 0.05$), and positively correlated with the changes in U-Kal ($P < 0.05$) and U-Na ($P < 0.01$). The change in U-Kal

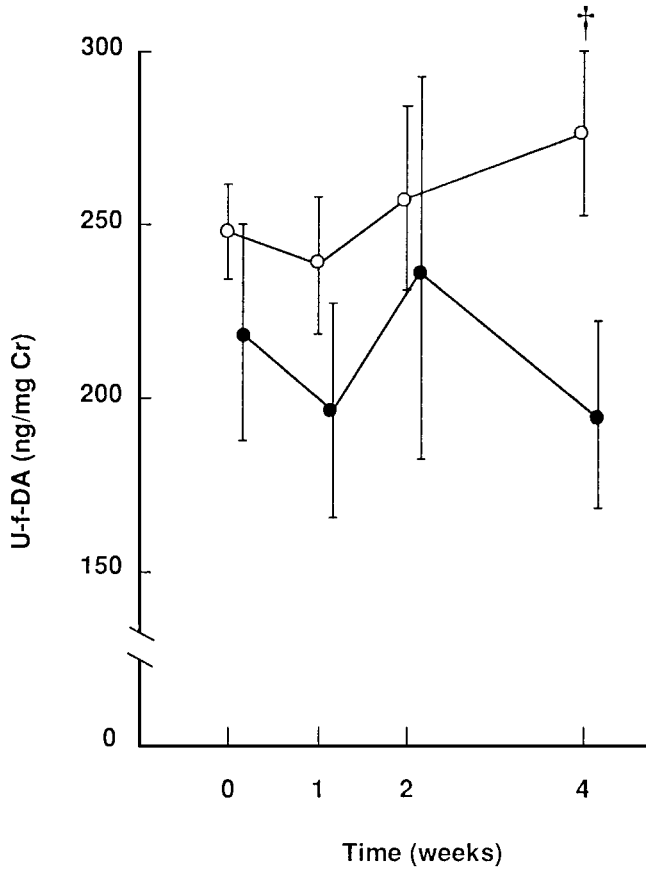

Figure 2 Changes in urinary free dopamine excretion between the exercise (○) and non-exercise (●) groups. U-f-DA, urinary free dopamine. Values are expressed as mean ± s.e.m. †$P < 0.05$ *vs* non-exercise group.

Table 3 Changes in humoral variables in the subjects

Variables	*Exercise group (n = 16)*		*Non-exercise group (n = 13)*	
	Week 0	*Week 4*	*Week 0*	*Week 4*
PRA (ng/mL per hr)	0.83 ± 0.15	0.76 ± 0.12	0.77 ± 0.13	0.71 ± 0.18
P-DOPA (ng/mL)	1.2 ± 0.3	1.3 ± 0.1	1.1 ± 0.1	1.1 ± 0.1
P-f-DA (pg/mL)	13 ± 1	11 ± 2	—	—
P-t-DA (pg/mL)	3359 ± 898	2511 ± 268	—	—
P-f-NA (pg/mL)	395 ± 26	416 ± 24	394 ± 19	443 ± 35
P-t-NA (pg/mL)	1151 ± 71	1102 ± 63	—	—
U-DOPA (ng/mgCr)	21.6 ± 4.7	20.7 + 3.0	—	—
U-f-DA (ng/mgCr)	248 ± 14	276 ± 24†	220 ± 31	196 ± 27
U-t-DA (ng/mgCr)	1580 ± 331	1279 ± 126†	1039 ± 193	843 ± 125
U-f-NA (ng/mgCr)	47 ± 2	53 ± 3†	50 ± 14	36 ± 6
U-t-NA (ng/mgCr)	202 ± 21	193 ± 12††	208 ± 93	113 ± 15
U-Na (mEq/mgCr)	0.21 ± 0.02	0.22 ± 0.02	0.20 ± 0.03	0.18 ± 0.03
U-K (mEq/mgCr)	0.06 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.05 ± 0.02
U-kallikrein activity (ng kinin/min/mgCr)	173.0 ± 35.4	320.3 ± 63.3**	217.7 ± 33.7	223.5 ± 54.8
Renal DA formation rate [U-f-DA/(DOPAxCcr)]	1.37 ± 0.11	1.48 ± 0.11	—	—

Values are expressed as mean ± s.e.m. **$P < 0.01$ *vs* week 0; †$P < 0.05$, ††$P < 0.01$ *vs* non-exercise group. PRA, plasma renin activity; P-DOPA, plasma dopa; P-f-DA, plasma free dopamine; P-t-DA, plasma total dopamine; P-f-NA, plasma free noradrenaline; P-t-NA, plasma total noradrenaline; U-DOPA, urinary dopa; U-f-DA, urinary free dopamine; U-t-DA, urinary total dopamine; U-f-NA, urinary free noradrenaline; U-t-NA, urinary total noradrenaline; U-Na, urinary sodium; U-K, urinary potassium; U-Kallikrein activity, urinary kallikrein activity; Renal DA formation rate, renal dopamine formation rate.

was negatively correlated with the changes in SBP ($P < 0.05$) and DBP ($P < 0.05$), and positively correlated with the change in U-Na (Figure 3, $P < 0.01$). The change in U-Na was negatively correlated with the change in SBP ($P < 0.01$) (Table 4).

The ratio of urinary free DA to plasma (DOPA × Ccr), which reflects the conversion of plasma DOPA to DA in the kidneys, did not change significantly after 4 weeks in the exercise group, but it was positively correlated with the changes in U-f-DA ($P < 0.05$) and U-Na ($P < 0.05$) in the same period. It was also negatively correlated with the changes in SBP ($P < 0.01$) and MBP ($P < 0.05$) (Table 4). Similarly, the decrease in PVI after 4 weeks of exercise was not significant, but it was negatively correlated with the changes in U-f-DA ($P < 0.05$) and U-Na (Figure 3, $P < 0.05$) (Table 4). Stepwise regression analysis revealed that at week 4 U-Na was positively correlated with U-f-DA ($P < 0.05$).

Discussion

In the present study, we investigated the changes in the renal DA system in relation to other variables to confirm the role of the renal DA system in the BP-lowering effect of mild exercise training in the early phase.

We previously found a significant increase in U-t-DA as early as week 4 of exercise.[13] In a recent study, we also reported[15] that the change in U-f-DA from week 0 to week 2 was positively correlated with the change in U-Na from week 0 to week 2 in the exercise group. Moreover, from week 0 to week 2, the change in U-t-DA was negatively correlated with the change in DBP, and the change in U-Kal was negatively correlated with the change in SBP.

In the present study, U-f-DA tended to increase only in the exercise group. The time-course of changes in U-f-DA and U-t-DA also differed significantly between the two groups. The U-f-DA and U-t-DA were significantly higher in the exercise group than in the non-exercise group at week 4. U-Kal increased significantly after exercise for 4 weeks. These data suggest that mild exercise may activate the renal DA system, together with the renal kallikrein-kinin system, during the early phase of exercise.

Urinary kallikrein is known to be decreased in essential hypertensives.[27] In our previous study, the decreased urinary kallikrein in hypertensives was increased after exercise in correlation with the reduction of BP.[15] Although the mechanism of the increase of urinary kallikrein is unclear, DA infusion in essential hypertensives was reported to increase urinary kallikrein excretion.[28]

We next analysed the correlation between the change in urinary DA and other variables which might activate the renal DA system in the exercise group. The closer correlation between changes in U-f-DA rather than that of U-t-DA and other haemodynamic and humoral variables suggest the active free DA is better to investigate for the elucidation of the physiological role of DA. In the exercise group, the change in U-f-DA from week 0 to week 4 was negatively correlated with the changes in SBP and DBP, and positively correlated with the changes in U-Kal and U-Na. The change in U-Kal from week 0 to week 4 was negatively correlated with the changes in SBP and DBP, and positively correlated with the change in U-Na, which, in turn, negatively correlated with the change in SBP. The change in PVI was negatively correlated with the changes in U-f-DA and U-Na after exercise for 4 weeks. In the exercise group, cardiac index (CI) decreased significantly after exercise for 4 weeks, suggesting that the BP reduction was due to the reduction of CI. We could not show a significant increase of sodium excretion in the present study, probably because we did not strictly

Table 4 Correlation between changes (Δ) in BP or humoral variables from week 0 to week 4

	(Δ) *MBP*	*DBP*	*U-f-DA*	*U-t-DA*	*U-Kal*	*U-f-NA*	*U-t-NA*	*U-Na*	*P-f-DA*	*P-t-DA*	*P-f-NA*	*P-t-NA*	*PRA*	*PAC*	*Renal DA form.*	*PVI*
(Δ) SBP	0.85**	0.62**	−0.69**	−0.41	0.59*	−0.34	−0.51	−0.71**	0.36	−0.22	−0.22	−0.27	0.36	−0.23	−0.70**	0.40
MBP		0.93**	−0.73**	−0.35	−0.70**	−0.22	−0.44	−0.64**	0.25	0.01	−0.09	−0.01	0.51	−0.45	−0.68**	0.44
DBP			−0.58*	−0.26	−0.64**	−0.08	−0.28	−0.49	0.40	0.13	0.03	0.19	0.50	−0.41	−0.56**	0.45
U-f-DA				0.52*	0.55*	0.12	0.64**	0.73**	−0.31	0.17	0.03	0.17	−0.21	0.51	0.58*	−0.53*
U-t-DA					0.17	−0.13	0.78**	0.42	−0.24	0.63*	0.03	0.27	0.28	0.29	0.41	−0.30
U-Kal						−0.23	0.09	0.61*	−0.49	0.01	0.10	0.18	−0.51	0.47	0.41	−0.21
U-f-NA							−0.28	0.09	0.57*	−0.03	0.39	0.10	−0.07	0.31	0.39	−0.34
U-t-NA								0.57*	−0.17	0.34	−0.03	0.24	0.06	0.51	0.43	−0.31
U-Na									−0.35	0.08	0.18	0.26	−0.43	0.44	0.58*	−0.52*
P-f-DA										0.17	0.63*	0.43	0.31	−0.45	0.14	0.05
P-t-DA											0.18	0.27	0.62*	−0.27	0.29	−0.22
P-f-NA												0.63*	0.22	−0.24	0.43	−0.08
P-t-NA													0.10	−0.03	0.22	−0.12
PRA														−0.32	−0.12	0.18
PAC															0.01	−0.05
Renal DA form.																−0.55*

*$P < 0.05$,**$P < 0.01$. SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure; U-f-DA, urinary free dopamine; U-t-DA, urinary total dopamine; U-Kal, urinary kallikrein activity; U-f-NA, urinary free noradrenaline; U-t-NA, urinary total noradrenaline; U-Na, urinary sodium; P-f-DA, plasma free dopamine; P-t-DA, plasma total dopamine; P-f-NA, plasma free noradrenaline; P-t-NA, plasma total noradrenaline; PRA, plasma renin activity; PAC, plasma aldosterone concentration; Renal DA form., renal dopamine formation rate; PVI, plasma volume index.

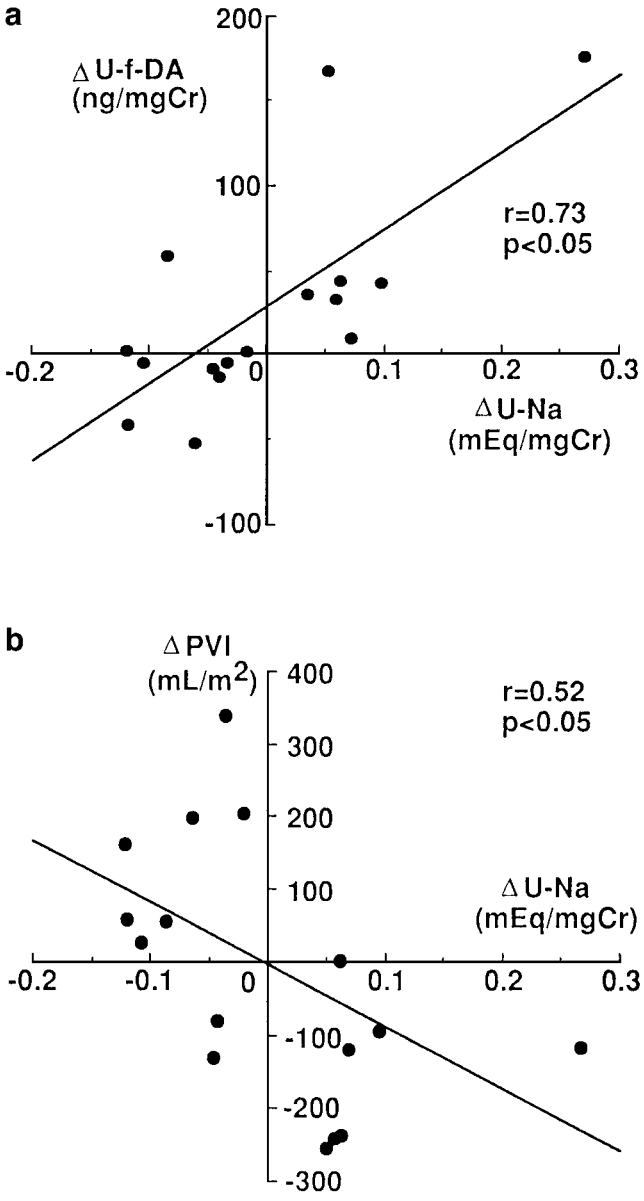

Figure 3 Correlations between changes (Δ; from week 0 to week 4) of urinary sodium excretion (ΔU-Na, mEq/mg creatinine) and urinary free dopamine (ΔU-f-DA, ng/mg creatinine) (**a**), and between changes of urinary sodium and plasma volume index (ΔPVI, mL/m^2) (**b**).

control daily intake of sodium and because sodium excretion was measured only once a week. Balance studies before and after exercise therapy may be necessary to detect natriuretic effect. As mentioned below, sodium intake is known to be an important regulator of urinary DA, and also, DA is known to reduce Na reabsorption at the proximal tubules to promote natriuresis. Thus, DA and Na can affect each other. If the sodium intake increased in the exercise group, it could increase BP and urinary DA. However, it is unlikely because we asked all patients of both groups to maintain their usual dietary habits. Although, correlation between two factors does not always mean a direct casual relation, a highly significant correlation between exercise-induced changes in BP and sodium excretion and between sodium excretion and PVI suggests the small, but not significant, natriuresis causally related to the reduction of plasma volume and BP. In addition, there were negative correlations between changes in BP and U-f-DA or U-Kal, both were well known to cause natriuresis. Therefore the BP reduction achieved by mild exercise in mild essential hypertensive patients may be attributed, at least in the early phase, to natriuresis resulting from activation of the renal DA and kallikrein-kinin systems.

Lee[29] reported that urine DA must be formed locally in the mammalian kidney from circulating DOPA. There were three main hypotheses at that time: (a) intrarenal deconjugation, (b) release from renal nerves, and (c) renal decarboxylation of plasma DOPA. The intervening years have reinforced the last view, and the alternative hypotheses have now been abandoned.[30–32] Thus, we now believe that urinary DA is produced mainly from plasma DOPA. However, the route of DOPA uptaken from plasma into tubular cells is unknown. Both filtered DOPA and peritubular interstitial fluid DOPA could account for this. Aromatic-L-amino-acid decarboxylase (L-AAAD), which is responsible for the synthesis of DA from plasma DOPA, has been identified at the renal cortex by histofluorescence techniques[33] and at the PCT[34,35] by biochemical studies. Hayashi *et al*,[36] using microdissected nephron segments, have also shown that L-AAAD activity is higher in the proximal convoluted tubules than in the proximal straight tubules. Under normal circumstances, there is a close relationship between urinary sodium and urinary DA, and dietary sodium appears to control renal DA synthesis.[37,38] Hayashi *et al*[39] reported that most of the increase in urinary DA seen following an increase in salt intake is due to non-neural sources, and derives from the proximal tubule. Moreover, there were no differences in glomerular filtration rate (GFR) between rats on low- and high-salt diets, despite a three-fold increase in DA production in the rats on the high-salt diet, suggesting that the effect of this renally produced DA is tubular rather than due to changes in renal haemodynamics. If urinary DA is formed from the uptake of circulating DOPA and is decarboxylated in the kidney, then inhibition of L-AAAD should decrease urinary DA excretion, as has actually been reported.[40–42] DA is known to suppress Na^+, K^+-ATPase activity in the proximal convoluted tubule (PCT) and the thick ascending limb of the loop of Henle.[43] The Na^+, K^+-ATPase is located mainly on the basolateral membranes, where the stimulatory effect of DA on phospholipase C predominates, resulting in activation of protein kinase C and inhibition of Na^+, K^+-ATPase activity. It was also reported that the stimulatory effect of DA on adenylate cyclase activity predominates at the brush-border membrane, resulting in an inhibition of Na^+, H^+ antiport activity. It is possible, therefore, that the natriuretic effect of DA may be due to the inhibition of Na^+, H^+ antiportor and/or Na^+, K^+-ATPase activities by DA.

We evaluated the ratio of urinary free DA to filtered DOPA (calculated by plasma DOPA × Ccr), as the measure of the conversion of plasma DOPA to DA in the kidneys,[28] and the change between weeks 0 and 4 was positively correlated with the changes

in U-f-DA and U-Na, and negatively correlated with the changes in SBP and MBP. The filtered DOPA remained unchanged and urinary DOPA excretion decreased significantly in the examination of the conversion of (plasma DOPA to dopamine) after 4 weeks exercise. These data suggest that mild exercise activated L-AAAD in the proximal cell and hence increased DA generation in the kidneys. Renal DA, in turn, must have inhibited Na^+ reabsorption in the proximal tubules by inhibiting Na^+, K^+-ATPase and/or Na^+, H^+ antiporter, resulting in natriuresis which brought about a reduction in BP after 4 weeks of exercise.

Other variables which have an influence on the renal DA system, such as PRA, plasma aldosterone concentration, and ANP, also remained unchanged during 4 weeks of exercise. The lack of a well established correlation between PRA and U-Na may be explained by the fact that patients in this study had relatively low PRA and the change in U-Na might not be sufficient enough to alter PRA.

The most important methodological limitation of this study is the only once a week collection of 24-h urine, which may already include inaccuracy of collection due to patients' wrong handling. Although, urinary variables were corrected by creatinine, the more frequent collections and/or well-controlled balanced studies are necessary to confirm the effect of exercise on urinary variables. As well known, however, the pathogenesis of essential hypertension is heterogeneous and the anti-hypertensive mechanism of exercise is multifactorial. Thus, we cannot expect uniform change after exercise in all patients.

In summary, mild exercise in mild hypertensive patients brought about BP reduction, in agreement with our previous findings. This reduction was found to be accompanied by activation of the renal DA and kallikrein-kinin systems, which was positively correlated with the increase in U-Na and negatively correlated with the decrease in BP. It is suggested, therefore, that the BP reduction achieved during the early phase of mild exercise training in mild essential hypertensive patients is due, at least in part, to natriuresis through activation of the renal DA system by the activation of L-AAAD, as well as the kallikrein-kinin system.

Acknowledgements

We would like to thank Y Saito, R Hayashi, and K Marui for their skilful technical and secretarial services. We would also like to thank M Hayama for her help with the exercise programme.

This work was sponsored and supported by a Research Grant from the Foundation for Total Health Promotion.

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