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CLINICAL INVESTIGATION

Potassium and norepinephrine- or angiotensin–mediated pressor control in pre-hypertension

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Potassium and norepinephrine- or angiotensin–mediated pressor control in pre-hypertension. Blood pressure (BP), plasma electrolytes, renin, aldosterone, angiotensin II (AII) or catecholamines, the chronotropic effects of intravenous isoproterenol, norepinephrine (NE) or AII, the pressor responses to NE or AII, and the relationship between plasma AII and aldosterone concentrations were studied before and after 10 days of dietary supplementation with potassium 100 mmol/day, in normotensive members of normotensive ($N = 12$) or hypertensive ($N = 12$) families, and 11 patients with borderline essential hypertension. Under control conditions, the pressor responsiveness to NE was significantly enhanced in normotensive with positive family history for hypertension and hypertensive subjects; the other variables were comparable in the groups. After potassium supplementation, plasma potassium, renin, aldosterone or AII, and the relationship between AII and aldosterone levels increased significantly, while body weight, plasma catecholamines, the chronotropic effects of isoproterenol, AII or NE, the pressor effects of AII and plasma clearance of AII or NE were unchanged in all groups. In normotensive members of hypertensive families and patients with hypertension, BP was decreased and the exaggerated pressor responsiveness to NE was normalized; these variables were not modified in normotensive members of normotensive families. These observations are consistent with a potassium–remediable disturbance in NE- but not AII-dependent regulation of BP in the pathogenesis of essential hypertension.

Potassium (K^+) is involved in the regulation of blood pressure (BP) and perhaps also in the pathogenesis of essential hypertension. In the experimental animal, dietary K^+ supplementation blunted or even prevented the rise in BP caused by DOCA [1] or a high sodium intake [2–4] in spontaneously hypertensive rats [5]. In humans a high K^+ diet may reduce BP in normotensive offspring of hypertensive families [6–8] and improve established essential hypertension [6, 8–12]. Moreover, the antihypertensive effect of K^+ is particularly apparent on a high and blunted on a low sodium diet [12].

The BP-lowering mechanisms of dietary K^+ supplementation during high sodium intake are poorly understood. The regulatory abnormality that already exists in many normotensive offspring of hypertensive families is at least in part characterized by an exaggerated cardiovascular reactivity to norepinephrine (NE) in the presence of normal plasma catecholamine, renin and angiotensin II (AII) levels, unaltered responsiveness of BP and plasma aldosterone to AII, and a yet normal blood volume and exchangeable sodium [13–15]. In borderline or established essential hypertension, the disturbance in noradrenergic reactivity [16–19] may be complemented further by a tendency for slightly–increased plasma catecholamine concentrations [20] and probably a secondary increase in BP-responsiveness to AII [18], while aldosterone responses to AII were variably found to be enhanced [21], normal [22, 23] or even blunted [24].

Previous reports suggested that an increase in dietary K^+ intake may promote its antihypertensive action by enhancing natriuresis [3, 9], modulating baroreflex sensitivity [7], direct vasodilatation [3, 25] or lowering cardiovascular reactivity to NE [8] or AII [26]. The effects of a high K^+ intake on AII-mediated BP control and aldosterone responsiveness have not been assessed simultaneously with noradrenergic BP control. Such an aproach was chosen for the present investigation in young untreated patients with borderline essential hypertension and normotensive subjects with a negative or positive family history of essential hypertension (FHH).

Methods

Twelve, healthy normotensive volunteers with a negative FHH, 12 healthy normotensive volunteers with a positive FHH, and 11 patients with yet untreated essential hypertension were studied under outpatient conditions. Their age, sex and body habitus appear in Table 1.

The family tree was constructed carefully for each normotensive subject [13] and information on BP was obtained both by questioning the subjects and their families as well as directly from the family doctor and their medical records. The FHH was considered to be positive if at least one of both parents or any existing sibling had essential hypertension [13, 27]. In the subjects classified as having a negative FHH, both parents or any existing sibling had no known previous episodes of high BP, and a normal BP documented on medical record at least once in the year preceeding the investigation; there was also no evidence of hypertension in the grandparents of these subjects, although the latter information was incomplete in two. Parents or siblings of the normotensive subjects were considered as hypertensive if their untreated supine or sitting BP was consistently and repeatedly greater than 160/95 mm Hg before age 60 years. In contrast they were considered as normotensive if their BP was repeatedly less than 140/90 mm Hg before age 65 years and less than 160/95 mm Hg after age 65 years. The patients

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Table 1. Basal values of blood pressure, electrolytes and endocrine variables under basal dietary conditions or after dietary supplementation with potassium (mean ± SD)

	Normotensive members of				Patients with borderline essential hypertension	
	normotensive families		hypertensive families			
	basal K^+ diet	high K^+ diet	basal K^+ diet	high K^+ diet	basal K^+ diet	high K^+ diet
N	12		12		11	
Sex, *male/female*	7/5		5/7		4/7	
Age, *years*	22.8 ± 3.3		22.9 ± 3.4		27.3 ± 6.7	
	1.73 ± 0.07		1.73 ± 0.07		1.74 ± 0.11	
Weight, *kg*	62.3 ± 8.5	61.1 ± 9.3	64.3 ± 12.1	64.0 ± 12.2	71.0 ± 11.3	70.5 ± 10.6
Heart rate, supine, *beats/min*	63 ± 11	62 ± 6	64 ± 7	62 ± 5	63 ± 8	62 ± 5
Blood pressure, supine, *mm Hg*						
systolic	111 ± 9	110 ± 10	113 ± 8	107 ± 8[a]	132 ± 15[d]	126 ± 15[a]
diastolic	70 ± 7	70 ± 10	73 ± 6	70 ± 8	89 ± 9[d]	84 ± 11[a]
mean	83 ± 7	83 ± 9	86 ± 6	82 ± 6	103 ± 11[d]	98 ± 12[a]
Plasma sodium, *mmol/liter*	141 ± 2.5	140 ± 1.5	140 ± 2.0	139 ± 2.0	140 ± 1.2	139 ± 2.2
potassium, *mmol/liter*	3.90 ± 0.16	4.14 ± 0.17[b]	4.15 ± 0.19	4.35 ± 0.45[a]	4.20 ± 0.24	4.52 ± 0.21[b]
total calcium, *mmol/liter*	2.21 ± 0.06	2.26 ± 0.06	2.30 ± 0.10	2.29 ± 0.09	2.24 ± 0.10	2.27 ± 0.05
norepinephrine, *ng/liter*	171 ± 61	193 ± 110	195 ± 73	184 ± 78	200 ± 88	156 ± 80
epinephrine, *ng/liter*	37 ± 20	26 ± 23	41 ± 32	39 ± 36	49 ± 25	36 ± 26
renin activity, *ng/ml/hr*	0.95 ± 0.39	1.23 ± 0.53[a]	0.85 ± 0.41	1.22 ± 0.43[a]	0.82 ± 0.44	1.08 ± 0.51[a]
angiotensin II, *ng/liter*	13.1 ± 5.0	16.6 ± 6.4[a]	11.0 ± 6.9	12.5 ± 5.0	9.70 ± 4.1	12.7 ± 3.5[a]
aldosterone, *ng/liter*	62 ± 25	115 ± 59[a]	73 ± 46	169 ± 86[a]	82 ± 64	143 ± 84[a]
Urinary sodium, *mmol/24 hr*	141 ± 89	164 ± 82	159 ± 47	150 ± 40	166 ± 80	173 ± 73
potassium, *mmol/24 hr*	71 ± 33	161 ± 48[c]	75 ± 25	170 ± 36[c]	67 ± 24	159 ± 53[c]
Creatinine clearance, *ml/min/1.73 m²*	95 ± 18	99 ± 22	99 ± 25	102 ± 28	93 ± 17	97 ± 15

[a] $P < 0.05$ versus basal dietary conditions (by paired *t*-test)
[b] $P < 0.025$ versus basal dietary conditions (by paired *t*-test)
[c] $P < 0.01$ versus basal dietary conditions (by paired *t*-test)
[d] $P < 0.025$ versus normotensive members of normotensive or hypertensive families (by analysis of variance using the Bonferroni adjustment)

with borderline hypertension had repeated BP values between 140/90 and 160/95 mm Hg and sometimes below under outpatient conditions, and secondary forms of hypertension were excluded by the usual tests. No female subject was on hormonal contraceptives. All subjects were informed about the investigative character of the study and gave their informed consent. They were instructed to continue their usual diet but without very salty foods or adding salt to their food, starting at least 14 days before the control study; using this dietary instruction, 24 hour urinary sodium and K^+ excretions in 90 healthy subjects studied previously averaged 136 and 65 mmol, respectively [28].

Special studies were performed after 14 days of basal dietary condition and after 10 days of oral supplementation of the diet with K^+, 100 mmol/day, using slow tablets of potassium chloride, 0.75 g each, in three daily doses. Under both conditions, 24 hour urine was collected for determination of sodium, K^+ and creatinine excretion rates, and infusion of NE or AII were carried out in a morning after overnight fast with the participants resting throughout in a supine position [14, 19]. After a 60 minute equilibration period with slow intravenous infusion of 5% dextrose solution (0.1 ml/min), basal BP and heart rate were measured and blood samples were drawn through an indwelling intravenous cannula (placed at least 30 minutes previously on the arm controlateral to the infusion) for determination of basal plasma sodium, K^+, total calcium, creatinine, NE and epinephrine. These basal measurements were obtained between 8 and 9 a.m. The dextrose solution was then replaced by a solution containing levarterenol bitartrate in 5% dextrose (NE base, 10 to 20 μg/liter). NE was infused at stepwise increasing dose rates which were maintained for 20 minutes each. All subjects received successive dose rates of 20, 40 and 100 ng/kg/min, and, when the NE-induced increase in mean BP did not reach 20 mm Hg, 200 ng/kg/min. During the last 10 minutes of each infusion step, BP and heart rate were recorded every minute; at the end of each infusion step blood samples were obtained from the arm contralateral to the infusion for determination of NE. The NE infusion was then replaced by 5% dextrose solution at slow rate for 45 minutes. At the end of this second equilibration period, BP and heart rate were measured and blood was drawn for determination of plasma renin activity, aldosterone and AII levels. The dextrose solution was then replaced by a solution of (Val^5)-AII (Hypertensin, Ciba Geigy, Summit, New Jersey, USA) in 5% dextrose (AII, 1 to 2 μg/liter), which was infused at stepwise increasing dose rates of 2, 4, and 10 ng/kg/min, and, when the AII-induced increase in diastolic BP did not reach 20 mm Hg, 20 ng/kg/min, for 20 minutes each. BP and heart rate were monitored as described above, and blood samples were obtained from the arm contralateral to the infusion at the end of each infusion step for determination of plasma AII and aldosterone concentrations.

Thereafter, the subjects were allowed to stand up for emptying their bladder and having a light breakfast. After an additional 20 minute equilibration period during which the subjects rested and received a slow intravenous infusion of 5% dextrose, boli of 1, 2, 4 and 8 nmol isoproterenol hydrochloride (5 to 20 nmol/liter) were injected and the heart rate was monitored continuously. When the maximal increase in heart rate did not

reach 30 beats/min, further doses of 16 and 32 nmol isoproterenol were injected.

BP was measured with the automated recorder Physiometrics SR 2, which detects Korotkoff sounds by microphone and converts them to mechanical signals recorded on a graduated disk. In a series of paired readings, this automated device did not show marked deviations from readings by the standard mercury sphygmomanometer [29]. Before each infusion study with NE or AII, respectively, the machine was mechanically adjusted to give values equal to those of the mercury manometer. Mean arterial pressure was calculated as the sum of diastolic and one third of pulse pressure. Each recorded value was the mean of at least eight measurements. For isoproterenol sensitivity testing, the heart rate was continuously monitored using an electrocardiogram; resting (pre-infusion) heart rate and heart rate response to isoproterenol were calculated from the three shortest R-R intervals before and following injection. The chronotropic dose of isoproterenol that increased heart rate 25 beats/min was obtained from dose–response curves relating changes in heart rate to corresponding doses of isoproterenol. Pressor effects of NE or AII were assessed by plotting individual changes in mean (NE infusion study) or diastolic (AII infusion study) BP versus corresponding NE or AII infusion rates or associated changes in plasma NE or AII concentrations; the pressor dose of NE [16] or AII [30] was defined as the dose required to increase mean (NE) or diastolic (AII) BP 20 mm Hg. Moreover, the increase in circulating NE or AII to elevate BP 20 mm Hg was calculated [8]. The responsiveness of plasma aldosterone to infused AII was assessed by plotting individual changes in plasma AII versus corresponding changes in plasma aldosterone; the increase in plasma AII level necessary to elevate plasma aldosterone by 200 ng/liter was derived. As an appropriate index of baroreflex integrity, individual heart rate responses during NE or AII infusion were plotted against the changes in mean BP; the heart rate response to an increase in mean BP of 20 mm Hg was calculated [8]. The total plasma clearance of NE or AII was calculated dividing infusion rates by the associated change in plasma concentration of NE or AII, respectively [8, 31]. The mean of three to four calculated clearances was recorded, clearance values being similar during lower and higher infusion rates [31]. Plasma and urinary sodium and K^+ were measured by flame photometer, creatinine by autoanalyzer, total plasma calcium by atomic absorption spectrophotometry, NE and epinephrine by a radioenzymatic assay [32], and plasma renin activity [33], AII [34] and aldosterone [35] by radioimmunoasay, as reported previously from this laboratory [14, 36].

The three study groups were compared with each other by analysis of variance using the Bonferroni adjustment [37], while comparisons between the two study conditions were made by two–tailed paired *t*-test [38]. The infused doses of NE or AII were cumulatively related with the corresponding blood levels using bilogarithmic regressions. The calculated regression equations were compared with each other by analysis of covariance [39]. Many biological measurements follow a Gaussian distribution only after logarithmic transformation [40]. For this reason the homogeneity test of Pearson [41] was performed both using absolute values or the natural logarithmic transformation. Based on this test the natural logarithmic transformation was used for analysis of doses and plasma levels of NE or AII, for plasma epinephrine, aldosterone and renin levels, as well for doses of isoproterenol. Significance was assumed when $P < 0.05$, and results are given as mean and standard deviation.

Results

Basal (pre-infusion) blood pressure, electrolytes and plasma levels of endocrine variables

Under basal dietary conditions mean body weight and BP were quite similar in the normotensive groups with negative or positive FHH (Table 1). Body weight tended to be slightly higher in the patients with borderline hypertension. Heart rate, urinary excretion rates of sodium and K^+, creatinine clearance, and plasma levels of sodium, K^+, calcium, NE, epinephrine, renin activity, AII and aldosterone did not differ significantly among the three groups.

Following supplementation with K^+, 100 mmol/day, urinary K^+ excretion rates increased at a comparable degree in the normotensive subjects with negative (by 90 ± 31 mmol/day) or positive FHH (by 95 ± 25 mmol/day) and patients with borderline hypertension (by 92 ± 29 mmol/day) (Table 1). Systolic, diastolic and mean BP were unchanged in normotensive subjects with negative FHH. However, systolic BP decreased significantly ($P < 0.05$) in normotensive members of hypertensive families (−4 ± 5 mm Hg) and patients with borderline hypertension (−5 ± 5 mm Hg), and a similar tendency was noted for diastolic (−3 ± 7 mm Hg, NS, and −4 ± 8 mm Hg, $P < 0.05$, respectively) and mean BP (−4 ± 9 mm Hg, NS, and −5 ± 8 mm Hg, $P < 0.05$, respectively). Plasma K^+, aldosterone and renin activity rose significantly ($P < 0.05$ to < 0.025) in all study groups, plasma AII also tended to increase. Body weight, creatinine clearance, plasma and urinary sodium, and plasma calcium, NE and epinephrine values were not significantly changed during high K^+ intake (Table 1).

Metabolism of infused norepinephrine or angiotensin II

The metabolism of infused NE or AII, judged both by their total plasma clearance and by the relationship between cumulated infusion rates and concomitant plasma concentration (Table 2), did not differ among the three study groups. Moreover, high K^+ intake did not significantly modify these variables.

Effects of norepinephrine or angiotensin II infusion

During basal K^+ intake, the dose of infused NE required to elevate mean BP 20 mm Hg was reduced by 30% in normotensive members of hypertensive families and by 48% in borderline hypertensive patients (Table 3) as compared with normotensive subjects with negative FHH; the amount of plasma NE required to elevate mean BP 20 mm Hg was in the two former groups decreased by 50% and 38%, respectively. The dose of infused AII required to elevate diastolic BP 20 mm Hg, the amount of plasma AII required to elevate diastolic BP 20 mm Hg, and the changes in plasma AII associated with an increase in plasma aldosterone of 200 ng/liter were comparable in all study groups.

Compared with basal dietary conditions, a high K^+ diet increased, in the normotensive members of hypertensive families and patients with borderline hypertension, the pressor dose of infused NE by 68% and 35%, respectively, and the amount of

Table 2. Calculated total plasma clearance (mean ± SD), and intercept and correlation coefficient of bilogarithmic regressions relating cumulated infused doses and corresponding blood levels of norepinephrine or angiotensin II obtained during infusion studies

	Norepinephrine infusion				Angiotensin II infusion			
	Plasma clearance *ml/min/kg*	Intercept	Slope	Correlation coefficient	Plasma clearance *ml/min/kg*	Intercept	Slope	Correlation coefficient
Normotensive members of normotensive families (N = 12)								
basal potassium diet	88 ± 38	2.51	0.95	0.91	105 ± 43	2.78	0.91	0.90
high potassium diet	98 ± 31	2.56	0.93	0.78	108 ± 57	3.01	0.80	0.84
Normotensive members of hypertensive families (N = 12)								
basal potassium diet	90 ± 28	2.25	0.84	0.76	119 ± 50	2.52	1.01	0.87
high potassium diet	104 ± 34	2.23	0.79	0.78	117 ± 71	2.83	0.87	0.90
Patients with borderline essential hypertension (N = 11)								
basal potassium diet	79 ± 37	2.69	1.02	0.78	129 ± 77	2.42	1.09	0.79
high potassium diet	94 ± 45	2.55	0.96	0.85	102 ± 46	2.80	0.86	0.91

Calculated clearance values were compared with each other by paired t-test (comparison between the two study conditions) and analysis of variance using the Bonferroni adjustment (comparison among the three study groups) and were found not to differ. Regression equations were compared with each other by analysis of covariance according to Duncan and not found to differ significantly. All regressions were statistically significant ($P < 0.001$).

Table 3. Pressor and endocrine effects of exogenous norepinephrine or angiotensin II (mean ± SD)

	Normotensive members of				Patients with boderline essential hypertension	
	normotensive families		hypertensive families			
	basal K^+ diet	high K^+ diet	basal K^+ diet	high K^+ diet	basal K^+ diet	high K^+ diet
N	12		12		11	
Dose of infused norepinephrine to elevate mean arterial pressure 20 mm Hg, *ng/kg/min*	134 ± 81	120 ± 94	96 ± 43	125 ± 61[a]	69 ± 34[d]	118 ± 56[b]
Increase in plasma norepinephrine to elevate mean arterial pressure 20 mm Hg, *ng/liter*	1675 ± 1082	1607 ± 1150	829 ± 410[d]	1489 ± 981[b]	1015 ± 676[c]	1670 ± 1167[b]
Dose of infused angiotensin II to elevate diastolic arterial pressure 20 mm Hg, *ng/kg/min*	10.3 ± 6.4	9.5 ± 4.7	8.4 ± 3.3	10.0 ± 5.3	11.2 ± 6.8	8.9 ± 4.9
Increase in plasma angiotensin II to elevate diastolic arterial pressure 20 mm Hg, *ng/liter*	139 ± 108	108 ± 51	120 ± 65	130 ± 111	141 ± 74	134 ± 96
Increase in plasma angiotensin II associated with an increase in plasma aldosterone of 200 ng/liter *ng/liter*	126 ± 49	85 ± 48[b]	132 ± 72	96 ± 60[b]	115 ± 52	80 ± 39[a]

[a] $P < 0.05$ versus basal dietary conditions (by paired t-test)
[b] $P < 0.025$ versus basal dietary conditions (by paired t-test)
[c] $P < 0.05$ versus normotensive members of normotensive families (by analysis of variance using the Bonferroni adjustment)
[d] $P < 0.025$ versus normotensive members of normotensive families (by analysis of variance using the Bonferroni adjustment)

plasma NE associated with this pressor response by 62% and 75%, respectively (Table 3). Thus, both variables returned to the values observed in normotensive subjects without FHH during basal K^+ intake. While in this normotensive control group, pressor effects of NE were not modified by the high as compared with basal K^+ intake. Correspondingly, the curve relating changes in plasma NE and concomitant increases in mean BP following NE dose rates of 20, 40 and 100 ng/kg/min (the three infusion rates that each subject received) was unaltered in normotensive subjects with negative FHH and displaced to the right (towards values obtained in the normotensive control group) in normotensive members of hypertensive families and patients with borderline hypertension (Fig. 1). This displacement was statistically significant ($P < 0.05$) at the dose rate of 100 ng/kg/min.

Compared with basal dietary conditions, K^+ supplementation did not significantly modify the dose of infused AII or the increase in circulating AII required to elevate diastolic BP by 20 mm Hg in the three study groups (Table 3). The curve relating changes in plasma AII and concomitant increases in diastolic BP following AII dose rates of 2, 4 and 10 ng/kg/min (the three infusion rates that each subjects received) was also not significantly altered (Fig. 2).

Compared with basal K^+ intake the increase in plasma AII required to elevate the plasma aldosterone level by 200 ng/liter was reduced similarly ($P < 0.05$ to < 0.025) during a high K^+ intake in normotensive subjects with negative (−33%) or positive FHH (−27%) families and patients with borderline hypertension (−30%). The curve relating plasma AII and concomitant plasma aldosterone levels before and during AII infusion at

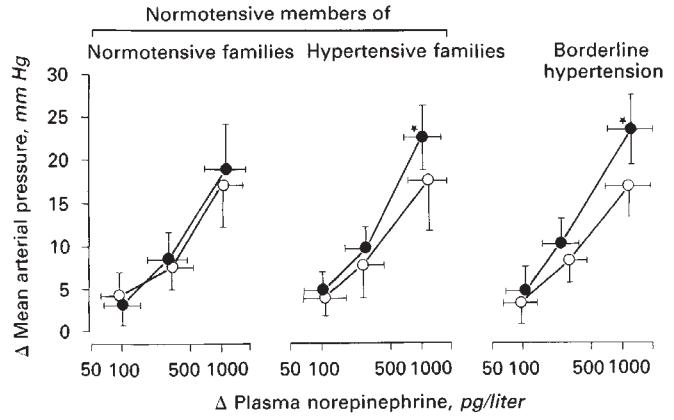

Fig. 1. *Relationship between Δ plasma norepinephrine and Δ mean arterial pressure during norepinephrine infusion at stepwise increasing dose rates of 20, 40 and 100 ng/kg/min under basal dietary conditions (closed circles) or after dietary supplementation with potassium (open circles) in the three study groups.* The far left symbol represents values at the end of the first norepinephrine infusion step; symbols thereafter represent data at the end of the following infusion steps. Bars represent the SD; some bars have been omitted for clarity; * $P < 0.05$ versus dietary control conditions.

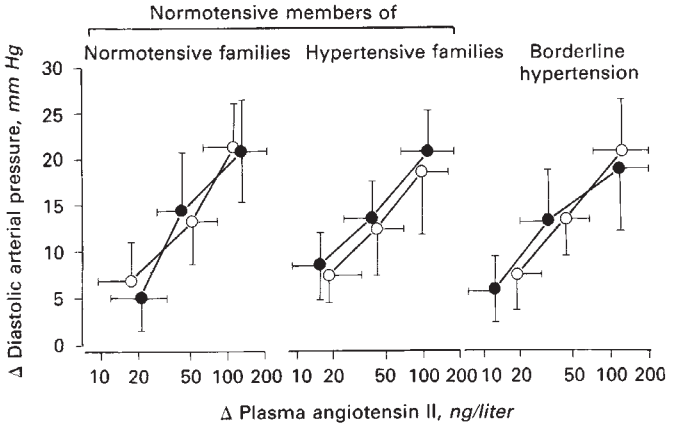

Fig. 2. *Relationship between Δ plasma angiotensin II and Δ diastolic arterial pressure during angiotensin II infusion at stepwise increasing dose rates of 2, 4 and 10 ng/kg/min under basal dietary conditions (closed circles) or after dietary supplementation with potassium (open circles) in the three study groups.* The far left symbol represents values at the end of the first angiotensin II infusion step; symbols thereafter represent data at the end of the following infusion steps. Bars represent the SD; some bars have been omitted for clarity.

dose rates of 2, 4 and 10 pmol/kg/min was significantly ($P < 0.05$) displaced upwards (Fig. 3).

Responses of heart rate

The heart rate responses to boli of isoproterenol or to rises in BP induced by infusion of NE or AII were quite similar in the three study groups during basal K^+ intake and were not significantly modified by a high K^+ diet (Table 4).

Discussion

The present findings indicate that supplementation of a usual "modern man" diet with K^+ improves in normotensive members of hypertensive families as well as patients with borderline hypertension a characteristic regulatory abnormality, namely, the pressor hyperresponsiveness to NE relative to endogenous plasma NE levels [13, 16–19]. In both groups the dietary K^+-induced improvement in cardiovascular NE hyperreactivity was accompanied by a slight decrease in BP. In contrast, an augmented potassium intake did not modify BP or NE responsiveness in normotensive control subjects with negative FHH, nor did it significantly alter AII pressor reactivity relative to circulating AII in any of the three groups. These observations are consistent with a K^+-remediable disturbance in NE- but not AII-mediated regulation in the pathogenesis of essential hypertension.

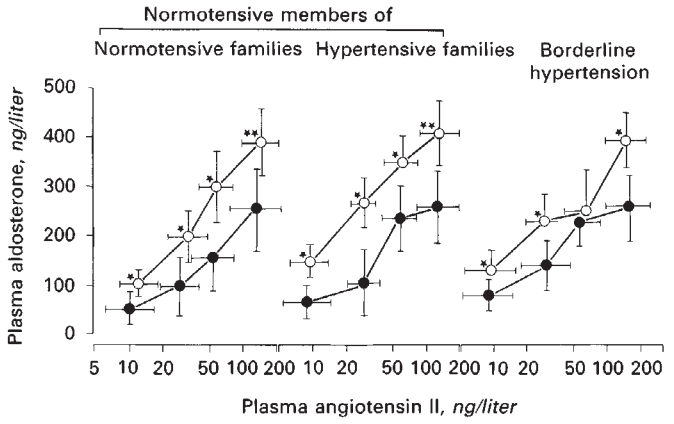

Fig. 3. *Relationship between plasma angiotensin II and plasma aldosterone before and during angiotensin II infusion at stepwise increasing dose rates of 2, 4 and 10 ng/kg/min under basal dietary conditions (closed circles) or after dietary supplementation with potassium (open circles) in the three study groups.* The far left symbol represents basal measurements before angiotensin II infusion; symbols thereafter represent data at the end of each successive infusion step of angiotensin II. Bars represent the SD; some bars have been omitted for clarity; *$P <$ 0.05; **$P < 0.025$ versus dietary control conditions.

K^+ is obviously a relevant factor in BP regulation. Our observations complement previous reports of an ameliorating effect of a high K^+ intake on BP in experimental or spontaneous hypertension [1–5], in some [6, 8–12] but not all [42] studies of human essential hypertension, and in normotensive offspring of hypertensive families [6–8], particularly when K^+ was added to a high sodium diet [12].

K^+ may in fact interact with various BP-regulating components. As expected [43, 44], basal plasma renin, AII and aldosterone levels, as well as the responsiveness of aldosterone to AII, were increased in the present study during high as compared with a lower K^+ intake. Nevertheless, since these adaptive changes were of similar magnitude in the three groups and pressor responses to infused AII seemed to remain largely commensurate for circulating plasma AII concentrations, the preferential BP-lowering effect of high K^+ diet in normotensive subjects with a positive FHH and borderline hypertensive patients could not be explained by a modification in angiotensinergic or aldosterone–mediated BP control. Pressor effects of AII were previously noted to be blunted following dietary K^+ supplementation in some patients with essential hypertension [26] and following treatment of potassium depletion in hemodialysis patients (P. Weidmann, M.H. Maxwell,

Table 4. Heart rate responses to isoproterenol boli or rise in arterial pressure during infusion with norepinephrine or angiotensin II (mean ± SD)

	Normotensive members of				Patients with borderline essential hypertension	
	normotensive families		hypertensive families			
	basal K^+ diet	high K^+ diet	basal K^+ diet	high K^+ diet	basal K^+ diet	high K^+ diet
N	12		12		11	
Isoproterenol bolus dose to increase heart rate by 25 beats/min, *pmol/kg*	107 ± 73	120 ± 84	99 ± 65	78 ± 61	102 ± 91	86 ± 59
Heart rate change associated with a rise in mean arterial pressure of 20 mm Hg during norepinephrine infusion study, *beats/min*	−9.4 ± 6.5	−8.1 ± 5.6	−12.1 ± 5.8	−11.7 ± 4.5	−10.0 ± 7.0	−10.8 ± 6.6
Heart rate change associated with a rise in mean arterial pressure of 20 mm Hg during angiotensin II infusion study, *beats/min*	−5.2 ± 3.1	−5.5 ± 3.6	−6.3 ± 4.0	−7.0 ± 3.9	−5.0 ± 3.1	−4.8 ± 3.5

unpublished observations); nevertheless, the lack of simultaneous plasma AII measurements does not allow a judgement of the net influence of K^+ on integrated angiotensinergic control in these studies. The differential influence of K^+ on vascular and adrenal–cortical responsiveness to AII in all three groups in the present investigation is probably related to a varying response of AII receptor number or affinity in the two target organs [45, 46]. With regard to adrenergic BP regulation, it has been suggested that dietary K^+ supplementation might, in patients with essential hypertension and subjects with positive FHH, also slightly lower plasma NE [6, 10]. However, plasma concentrations of epinephrine and NE as well as heart rate were not altered by high K^+ intake in the present and some previous studies [7, 26].

Several additional factors must be considered as potential mechanisms of the K^+-mediated improvement in pressor responsiveness to NE in the FHH positive setting of "pre-hypertension" and in borderline hypertension. These include the uptake of NE into sympathetic nerve terminals, the plasma clearance of NE [31], the sensitivity of the baroreflex, the body sodium–blood volume state [47], morphological changes in the blood vessel wall/lumen ratio [48], and a functional change of cardiovascular adrenergic receptors or intracellular components. Some controversed data suggest that the neuronal reuptake of NE may be enhanced by K^+ [10, 49]. The relationship between NE infusion rates and concomitant plasma NE levels and the plasma NE clearance were unaltered during dietary K^+ supplementation in our three study groups, thus providing little support for this hypothesis. The baroreflex sensitivity, as judged from responses of heart rate to NE-induced rises in arterial BP, was also not modified. A previous report of augmented baroreflex sensitivity during dietary K^+ supplementation in 10 normotensive members of hypertensive families is difficult to judge, since NE was infused during five minutes only [7]. The latter may not have allowed achievement of a steady state for NE and BP levels, while the 20 minute duration of each NE infusion step in the present study should fulfill this prerequisite. Body sodium tends to decrease during K^+ loading [2, 9, 26]. In our study groups, plasma and urinary sodium values and body weight were not consistently changed after 10 days of high K^+ intake, thus indicating that extracellular sodium–fluid volume depletion could not explain the selective effect of K^+ supplementation on NE reactivity and BP observed in normotensive subjects with positive FHH or parents with borderline hypertension. The same conclusion applies to pressure elicited variations in vascular wall thickness [48] which are not likely to exist already, and account for the selective NE hyperreactivity in the FHH positive setting of pre-hypertension and which, if they existed, would hardly be reversed within 10 days of high K^+ intake only.

Considering these aspects and the lack of an effect of K^+ supplementation on cardiac beta–receptor responsiveness, observed improvements in NE reactivity were probably at least in part mediated by functional changes of resistance vessels. Electrophysiological studies indicate that K^+ stimulates a cellular electrogenic pump, thereby hyperpolarizing the membrane and reducing calcium influx [49]. In fact elevation of extracellular K^+ within the physiological range lowered the resistance to blood flow of intact vascular bed and caused relaxation of isolated, vascular smooth muscle [25, 50], Furthermore, K^+ antagonized the vasoconstrictor effect of NE or acetylbetaethylcholine [51, 52]. In contrast, the influence of K^+ on the responsiveness of blood vessels to other vasoactive agents, including AII, is more controversial [49]. The differential effects of dietary K^+ supplementation on NE as compared with the AII-dependent BP control observed in the present study in pre-hypertensive subjects possibly indicate that the membrane hyperpolarization induced by K^+ selectively closed the calcium channels affected by NE but not those affected by AII. This hypothesis is sustained by the observation that NE induced vasoconstriction depends more on intracellular calcium than that induced by AII [53, 54]. Moreover, chronic pharmacological blockade of cellular calcium entry lowered in normotensive or borderline hypertensive subjects pressor–responsiveness to NE but not AII [55].

A disturbance in noradrenergic regulation seems to play an important role in the pathogenesis of essential hypertension. Alterations that may alone or concomitantly raise BP, include an increased central and/or peripheral sympathetic activity [56, 57], an alteration in cardiovascular adrenergic receptors [57, 58], enhanced receptor–effector coupling [59, 60], as well as secondary elevation in blood vessels reactivity due to hypertension–induced wall thickening [47]. The present study does not allow discrimination of whether the exaggerated NE reac-

tivity in normotensive members of hypertensive families [13, 14] or patients with essential hypertension [18] is promoted by dietary K^+ deficiency, or whether the beneficial effect of K^+ supplementation on NE responsiveness is rather unspecific. Whatever the exact interactions at the cellular level, a familial occurrence of NE hyperreactivity relative to existing sympathetic activity may predispose for the development of essential hypertension. Moreover, a selective improvement in noradrenergic control without lowered angiotensinergic influence may in turn be an important common principle underlying the antihypertensive action of such various treatments as dietary K^+ supplementation, thiazide-type agents [19, 61], calcium channel blockers [55] or sympatholytics [17, 62].

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