Effects of Dietary Potassium on the Hemodynamics and Plasma Norepinephrine Kinetics in Patients with Essential Hypertension

HIROFUMI OHASHI, M.D., YUKIO MIURA, M.D., SHINOBU KIMURA, M.D.
YUKI ISHIZUKA, M.D., TAKASHI SUGAWARA, M.D., SHUNICHI TORIYABE, M.D.
TAKAO NOSHIRO, M.D., MASAKI TAKAHASHI, M.D., NAOKI SANO, M.D.
HIROSHI WATANABE, M.D., AND KAORU YOSHINAGA, M.D.

The effects of dietary potassium on the hemodynamics and plasma norepinephrine (NE) kinetics were studied in 10 patients with borderline hypertension. Potassium supplement (96 mEq daily for 5–7 days) induced a significant ($p < 0.05$) fall in blood pressure and a slight decrease in cardiac output. Both urine volume and urinary sodium excretion increased significantly ($p < 0.05$) for a first few days following the potassium supplement. The baseline values of the half-time of the rapid NE removal from plasma was significantly delayed in the hypertensive patients (1.05 ± 0.06 min, $p < 0.05$) when compared with those (0.88 ± 0.04) in normal controls. Potassium supplement induced a significant rise in both plasma NE levels and NE outflow rate ($p < 0.01$) in the hypertensive patients, while their half-times were significantly shortened (0.89 ± 0.07 min, $p < 0.01$). The pressor responsiveness to exogenously infused NE tended to diminish during the potassium supplement. These findings indicate that a high potassium intake might accelerate the slowed neuronal NE uptake in the hypertensive patients, while a potassium-induced fall in blood pressure might exert a baroreflex stimulation of NE release. As a net result, an increased NE outflow into the circulation has been confirmed. It is likely that a natriuresis-induced volume contraction might be a predominant factor responsible for the early reduction of blood pressure during the high potassium intake.

A number of clinical and experimental studies have indicated that dietary sodium and potassium might play an important role in the pathogenesis of essential hypertension.^{1–7} An excessive intake of dietary potassium has been shown to prevent the development of the salt-induced animal hypertension^{8,9} as well as to lower the blood pressure in the hypertensive patients.^{10–13} The mechanisms underlying its

antihypertensive action are widely controversial, but several possibilities have been proposed: a direct vasodilatory effect,^{14,15} a natriuresis-induced volume contraction,^{11,12,16–18} a suppression of sympathetic nerve activity^{5,12,19} and an alteration of renin-angiotensin axis,^{20,21} etc. In our previous study, an intimate interaction between sodium balance and neuronal uptake of norepinephrine (NE) at the peripheral sympathetic nerve terminals has been suggested in patients with essential hypertension.⁷ It should be therefore interesting to examine whether a dietary potassium supplementation may have a substantial influence on the peripheral mecha-

Key Words:

Dietary potassium
Plasma NE kinetics
Essential hypertension

The Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan

This study was supported by a Grant-in-Aid for Scientific Research (No. 57570329, 59570345) from the Ministry of Education, Science and Culture, Japan.

Mailing address: Yukio Miura, M.D., The Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980, Japan

nisms of the sympathetic nerve system, and whether its altered function may play a role in the potassium induced changes of blood pressure.

To test these possibilities, the present study was designed to evaluate the effects of dietary potassium on the hemodynamics and plasma NE kinetics in patients with essential hypertension.

SUBJECTS AND METHODS

Subjects in this study consisted of 10 patients with borderline hypertension aged 20–51 years with a mean of 32 ± 3 (SEM) and 14 normal controls aged 19–44 years with a mean of 30 ± 2 . Patients were considered to be hypertensive when their blood pressures were found to be above 140 mmHg systolic or 90 mmHg diastolic, or both, during three consecutive visits to our clinic. No patient had congestive heart failure or impaired renal function (plasma creatinine < 1.5 mg/dl). Secondary forms of hypertension were excluded by usual diagnostic testings. Any medication relevant to cardiovascular or sympathetic nerve function was discontinued at least 2 weeks before the study. An informed consent was obtained from each subject after the outline of this study was explained.

Every normal subject was studied while they were receiving an ad libitum diet. All hypertensive patients were studied at two conditions: Six of them were studied first on an ordinary hospital diet and then 5–7 days after receiving a potassium-supplemented diet by KCl tablets (96 mEq daily), while the remaining 4 were studied on the reverse order. A first and second study were performed at intervals of 2 weeks. Daily variation in blood pressure, pulse rate and urinary excretion of sodium and potassium were measured consecutively for 5–7 days during each study.

Procedures

All subjects were allowed to take a light breakfast or lunch without caffeinated drinks and were asked to refrain from smoking at least 6 hours before the study. Studies were performed mostly in the early afternoon to minimize the effect of diurnal variation on plasma NE concentration. Subjects were studied while they were supine.

Intravenous catheters were placed in the antecubital veins of the left and right arms and

their patency was maintained by infusion of a small volume of 5% glucose solution, which were used for the L-NE infusion and blood sampling respectively. The blood pressure and pulse rate were recorded serially at 10-min intervals with an automated sphygmomanometer (Nippon Colin Co., BP 203X). After 60 min rest, a blood specimen for plasma NE assay was drawn through a venous catheter and a systemic blood flow rate was measured with a dye-dilution technique using a cardiac output computing system (Nihonkoden Co. MLC4100). The dye dilution curves were traced by an ear piece detector. Then L-NE bitartrate (Levophed, Brenon Lab. Inc.) diluted freshly with 5% glucose solution to 0.05 mg base/ml containing 0.1 mg of sodium bisulfite was infused with a Truth B-1 infusion pump (Eiko Co.) through a venous catheter. Blood pressure and pulse rate were carefully monitored at 3-min intervals throughout the infusion period. The infusion rate was gradually stepped up from 0.5 to 1.0, 2.0 and 4.0 $\mu\text{g}/\text{min}$ at 15-min intervals. The highest rate of the infusion was maintained for 20 min and a couple of blood specimens were taken through a venous catheter placed in the opposite arm 15 and 20 min after starting the highest infusion. Then, timed blood specimens for plasma NE assay were serially drawn 3, 5, 15 and 20 min after stopping the infusion. An aliquot of the L-NE solution was also assayed to confirm the expected L-NE concentration.

Plasma NE concentration was measured with our modified procedures of the sensitive fluorometric method reported elsewhere²² Serum and urinary concentrations of sodium and potassium were determined by the flame photometry.

Analysis of Plasma NE Kinetics

Preliminary experiments confirmed that plasma NE concentrations declined rapidly immediately after stopping the infusion and then more slowly. When plasma NE concentrations were plotted against time (t) on the semilogarithmic scale, their disappearance curves were at least biexponential and were compatible with the theory that exogenously infused NE is distributed in biological pools which can be defined kinetically by an open two-compartmental model^{7,23,24} Thus, based on the assumption that basal levels of plasma NE (PNE) remain constant, plasma NE concentrations after stopping the infusion, PNE (t), can be approxi-

Fig.1. The effects of dietary potassium supplementation (96 mEq daily) on urine volume (UV), urinary excretion of sodium (UNaV) and potassium (UKV) in the hypertensive patients.

TABLE I THE EFFECTS OF DIETARY POTASSIUM ON PLASMA NOREPINEPHRINE (NE) KINETICS IN PATIENTS WITH ESSENTIAL HYPERTENSION

Variables	Normotensive subjects (n = 14)	Hypertensive patients (n = 10)			
		Baseline	p-values*	During K supplement	p-values**
α	0.809 ± 0.038	0.682 ± 0.037	0.01	0.726 ± 0.084	0.01
β	0.090 ± 0.007	0.103 ± 0.012	NS	0.112 ± 0.005	NS
$T_{1/2}\alpha$ [min]	0.88 ± 0.04	1.05 ± 0.06	0.01	0.89 ± 0.07	0.01
$T_{1/2}\beta$ [min]	8.25 ± 0.57	7.45 ± 0.72	NS	6.28 ± 0.29	NS
Kel [/min]	0.757 ± 0.035	0.643 ± 0.034	0.01	0.751 ± 0.063	0.05
V_1 [ml/kg]	52.6 ± 2.9	74.1 ± 7.7	0.01	59.4 ± 6.8	0.05
Clearance rate [ml/min/kg]	39.2 ± 2.0	46.4 ± 3.8	NS	40.9 ± 1.6	NS
NE outflow rate [ng/min/kg]	5.06 ± 0.56	6.64 ± 1.05	0.01	8.15 ± 1.13	0.01
Plasma NE [pg/ml]	127 ± 11	133 ± 15	NS	209 ± 27	0.01
Body weight [kg]	58.6 ± 2.9	65.5 ± 1.8	NS	65.2 ± 1.8	0.1

* = versus normotensive subject, ** = versus baseline values.

Values in the Table are means $\pm$ SEM. K = potassium; NE = norepinephrine; α = the slope of α -phase; β = the slope of β -phase; $T_{1/2}\alpha$ = the half-time of α -phase; $T_{1/2}\beta$ = the half-time of β -phase; Kel = elimination constant; V_1 = the volume of central compartment.

mated by the following equation,

$$PNE(t) - PNE = Ae^{-\alpha t} + Be^{-\beta t}$$

where A and B are the intercepts on the ordinate

and α and β are the slopes of the two exponential components, when plasma NE concentrations are plotted on the semilogarithmic scale. Further analyses of kinetic values were performed ac-

Fig.2. The effects of dietary potassium supplementation (96 mEq daily) on the half-time of the rapid NE removal from plasma in the hypertensive patients.

Fig.3. The changes of plasma NE concentration and endogenous NE outflow rate in the hypertensive patients, while they were receiving an ad lib diet (closed squares) and a potassium-supplemented diet (closed triangles). The dotted lines illustrate the limits of the means ± 2 standard deviations defined in the normotensive controls.

cording to the mathematical methods reported elsewhere.^{7,23}

Statistics

All data are expressed as means $\pm$ SEM. When subjects had their own control values, a two-tailed paired t-test was used for statistical comparison of the results after confirming their normal distribution. Unpaired data were evaluated with a two-tailed t-test or an analysis of variance. Probability levels of 5% or less were considered significant.

RESULTS

Effects of Potassium Supplementation on Hemodynamics and Urinary and Serum Electrolytes

Mean blood pressure showed a slight but significant ($p < 0.05$) fall from 100 ± 4 to 95 ± 3 mmHg during the potassium administration, while the pulse rate remained unchanged. The decrease in blood pressure was associated with a slight decrease in cardiac indices from 2.80 ± 0.12 to 2.50 ± 0.26 L/min/m² during the potassium supplement, while the systemic vascular resistance tended to rise slightly from 35.9 ± 2.3 to 40.3 ± 3.5 mmHg/L/min/m².

Urine volume and urinary sodium excretion increased significantly ($p < 0.05$) for a first few days during the potassium administration, but returned to the baseline levels thereafter (Fig. 1), while an increased excretion of urinary potassium lasted throughout the period of potassium supplementation. Serum potassium also increased significantly ($p < 0.05$) from 4.20 ± 0.08 to 4.60 ± 0.20 mEq/L during the potassium administration, whereas serum sodium did not show any appreciable change throughout the study. Body weight decreased slightly from 65.5 ± 1.8 to 65.2 ± 1.8 kg during the potassium supplementation.

Effects of Potassium Supplementation on Plasma NE Kinetics

Table I summarizes the kinetic values of plasma NE in normotensive subjects and in the hypertensive patients with or without potassium supplementation. Of these baseline values, the slopes (α) for the rapid removal phase were significantly smaller in the hypertensive patients ($p < 0.05$) than in the normal subjects, which resulted in a significant delay of the calculated half-time of the rapid NE removal ($\ln 2/\alpha$) in the hypertensive patients ($p < 0.05$) as compared

with those in the normotensive subjects (Fig. 2). The slopes for the slower removal phase (β) and the overall clearance rates were not significantly different between the two groups. The calculated NE outflow rate into the circulation was significantly ($p < 0.01$) greater in the hypertensive patients than in the normal subjects.

The potassium supplementation gave rise to a definite influence on the plasma NE kinetics in the hypertensive patients studied. All of the patients showed a significant rise in plasma NE levels ($p < 0.01$) during the potassium supplementation (Table I, Fig. 3). The slopes (α) for the rapid removal phase became significantly greater ($p < 0.01$), and thereby their half-times were significantly shortened ($p < 0.01$) as compared with their control values (Table I, Fig. 2). The values of elimination constant (K_{el}), distribution volume (V_1) and overall clearance rate (CL) also tended to normalize during the potassium supplement (Table I). The calculated rate of endogenous NE outflow into the circulation rose significantly ($p < 0.005$) following the potassium supplementation (Table I, Fig. 3).

Cardiovascular Responses to Exogenously Infused NE

An exogenous NE infusion induced a gradual rise in blood pressure and a concomitant fall in pulse rates. While subjects were receiving an ad libitum diet, the highest rate of NE infusion raised mean blood pressure from 82 ± 2 to 107 ± 2 mmHg in normotensive subjects and from 96 ± 3 to 114 ± 3 mmHg in the hypertensive patients. During the potassium supplementation, the similar NE infusion induced a rise in mean blood pressure from 90 ± 3 to 108 ± 3 mmHg in the hypertensive patients. When the changes of mean blood pressure were plotted against the plasma NE concentrations expressed in the logarithmic scale, a linear positive correlation was observed between these two variables. The slopes of the regression lines tended to be steeper in the hypertensive patients (8.66 ± 1.29) than in the normal subjects (7.72 ± 0.50). During the potassium supplement, those slopes tended to diminish in the hypertensive patients (7.86 ± 1.19).

DISCUSSION

Plasma NE concentration has been used as a marker of sympathetic nerve activity.²⁵⁻²⁸ However, plasma NE is a small fraction of NE

released from the sympathoadrenal system and its concentration depends upon a balance among the rate of release, the volume of distribution and the rate of removal.²⁷⁻²⁹ It must be assumed, therefore, that their individual variations are negligible, when plasma NE levels are used for a comparison of sympathetic nerve activity between subjects. A kinetic analysis of plasma NE has been developed for the solution of these problems encountered.^{7,23,29-36}

In this study, we measured the plasma NE kinetics according to the steady state NE infusion techniques, which eliminate the distribution phase of exogenously infused NE and enable us to calculate the rate of NE release into and the rate of its removal from plasma.^{7,23,32} Since plasma NE infused exogenously disappears rapidly by the biexponential time course, an adoption of the two-compartmental open model was considered to be adequate for the mathematical analysis. Its precise applicability, however, necessitates several assumptions: the basal levels of endogenous plasma NE levels remain constant throughout the study period or their fluctuations are negligible as compared with those of infused NE in plasma. The endogenous NE release may be reduced in response to the elevation of blood pressure and/or to raised plasma NE itself, which may cause a suppression of sympathetic nerve activity by the baroreflex- or presynaptic α -adrenoceptor-mediated mechanisms.^{37,38} The basal concentrations of plasma NE used to be less than 10% of the steady state levels of infused NE in this study. Previous study also indicates that an endogenous plasma NE may decrease as much as 45 pg/ml or 42% of the basal levels when mean blood pressure is elevated to 18% above the baseline by intravenous infusion of phenylephrine.³⁸ It is therefore possible that the present study underestimated the plasma concentrations of exogenously infused NE as much as 5% or less at the steady state condition. During the postinfusion period, an endogenous NE release may fluctuate in response to the rapid changes in blood pressure and plasma NE, which may give rise to an erroneous estimation of the kinetic values. Although its individual variation could not be confirmed in this study, every experimental condition was kept similar between subjects and between studies. Relatively smaller variances of kinetic values for each group indicate that an individual variation of the endogenous NE release might not be so critical as to affect the calculated

values of plasma NE kinetics, enabling us to compare them between subjects.

Raised plasma NE has been shown to influence its own clearance,^{39,40} but others have reported unchanged clearance over a 6-fold infusion range (NE: 0.01–0.06 $\mu\text{g/kg/min}$);³⁵ a similar dose to the present study. Actually, the clearance rates calculated in this study, 39.2 ml/kg/min (1.36 L/min/m²) for normal subjects and 43.8 (1.58) for the hypertensive patients, were quite comparable to those values, 1.32 L/min/m² for normal subjects and 1.34 for the hypertensive patients, which were determined by the kinetic analysis using a subpressor amount of tritiated L-NE.²⁹ These findings indicate that the plasma NE clearance is fairly independent of the changes in plasma NE concentration and in hemodynamics observed in this study.

The most remarkable findings in this study were that a half-time of the rapid removal phase for exogenously infused plasma NE showed a significant delay in the hypertensive patients, and that this abnormality tended to be normalized during the supplement of dietary potassium. As the rapid removal of plasma NE has been indicated to depend mainly upon the process of the neuronal uptake,^{29,33} the present data lend support to the previous reports that an efficiency of the neuronal uptake is lowered in some patients with essential hypertension.^{7,29} Furthermore, this study demonstrated that an excessive potassium intake has a substantial influence on the neuronal mechanisms and ameliorates the delayed neuronal uptake of NE. A similar effect of high potassium feeding on the neuronal uptake has been observed in a study of spontaneously hypertensive rats.⁴¹

The potassium-induced changes of the neuronal uptake may be derived either from the direct actions of potassium ions on the neuronal cell membrane, or from the indirect actions on other mechanisms. It is well known that the neuronal NE uptake of NE is largely dependent upon the enzymatic process of Na-K ATPase in the neuronal cell membrane⁴²⁻⁴⁴; the NE uptake is facilitated by activation of the neuronal Na-K ATPase, while it is attenuated by enzyme inhibition. As a slight but significant rise in serum potassium levels was observed during the potassium supplementation, it can not be ruled out that an increase in extra- or intra-cellular potassium may activate the neuronal Na-K ATPase and facilitate the NE uptake. It is also possible to speculate that a natriuretic factor

in plasma, proposed as an inhibitor of Na-K ATPase,⁴⁴⁻⁴⁶ is counteracted by supplemented potassium ions. Potassium-induced diuresis and natriuresis observed in this study should be considered as an alternative factor accounting for these sequences, as reported previously.⁷ Raised plasma NE itself has been indicated to accelerate the plasma NE clearance, as mentioned above.^{39,40} In this study, a potassium supplementation caused a significant rise in plasma NE levels, but tended to decrease slightly the overall clearance in most patients studied. It remains unclear, however, whether this mechanism may have a substantial influence on the neuronal NE uptake.

Irrespective of the mechanisms that might underly the effects of potassium on the sympathetic neurons, an enhanced uptake of NE can be expected to reduce an amount of endogenous or exogenous NE which reaches the adrenergic receptors located in the cardiovascular system and thereby to attenuate the NE-stimulated vasoconstriction. In fact, the pressor responsiveness to exogenously infused NE tended to diminish during the potassium supplementation. However, the resting levels of plasma NE as well as the endogenous NE outflow rate into the circulation showed a parallel increase during the potassium administration, contrary to the above expectation. This contradiction might be explained by a dual effect of high potassium intake on the sympathetic nerve function. A high potassium intake ameliorated a slowed neuronal uptake, whereas either a fall in blood pressure or a natriuresis-induced volume contraction, which accompanied during the potassium administration, may induce a baroreflex-mediated stimulation of NE release from the sympathetic nerve terminals. The net influence on NE outflow into the circulation should depend on which effect predominates. Actually, the effects of a high potassium intake on plasma NE levels have been reported variously.^{5,11,12} These findings may also suggest that the experimental conditions might be of further importance in these sequelae. It is thus likely that an enhanced neuronal NE uptake could not be a sole factor accounting for the blunted pressor response to exogenous or endogenous NE, but other potential mechanisms, including an increased baroreflex-sensitivity,⁴⁷ an activation of Na-K ATPase in the vasculature⁴⁴⁻⁴⁶ or an alteration of adrenoceptors,⁴⁸ might play a role.

This study has confirmed a modest but significant reduction in blood pressure following the potassium administration. This reduction in blood pressure was associated with a slight decrease in the cardiac output, mainly by reduced stroke volumes, whereas the systemic vascular resistance tended to rise slightly. These hemodynamic changes indicate that natriuresis-induced volume contraction might be a predominant factor responsible for the reduction in blood pressure. A slight reduction of body weight in these subjects may also support this possibility. An enhanced neuronal NE uptake and a blunted pressor response to NE could be hypotensive, but a significant increase in both NE release and plasma NE levels observed during the potassium administration, might interfere with these hypotensive neural mechanisms. It is therefore unlikely that the neural components might play a principal role at least in the early reduction of blood pressure following the high potassium intake. It remains undetermined, however, whether those hypotensive neuronal mechanisms could be of importance in the longer-term effects of dietary potassium on the cardiovascular system.

REFERENCES

1. DAHL LK, LOVE RA: Evidence for relationship between sodium (chloride) intake and human essential hypertension. *Arch Intern Med* **94**: 525, 1954
2. KAWASAKI T, DELEA CS, BARTTER FC, SMITH H: The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. *Am J Med* **64**: 193, 1978
3. HADDY FJ: Mechanism, prevention and therapy of sodium-dependent hypertension. *Am J Med* **69**: 746, 1980
4. RANKIN LI, LUFT FC, HENRY DP, GIBBS PS, WEINBERGER MH: Sodium intake alters the effects of norepinephrine on blood pressure. *Hypertension* **3**: 650, 1981
5. PARFREY PS, VANDENBURG MJ, WRIGHT P, HOLLY JMP, GOODWIN FJ, EVANS SJW, LEDINGHAM JM: Blood pressure and hormonal changes following alteration in dietary sodium and potassium in mild essential hypertension. *Lancet* **i**: 59, 1981
6. FUJITA T, HENRY WL, BARTTER FC, LAKE RC, DELEA CS: Factors influencing blood pressure in salt-sensitive patients with hypertension. *Am J Med* **69**: 334, 1980
7. KIMURA S, MIURA Y, ADACHI M, ADACHI M, NEZU M, TORIYABE S, SUGAWARA T, ISHIZUKA Y, NOSHIRO T, TAKAHASHI M, OHASHI H, YOSHINAGA K: The effect of sodium depletion on plasma norepinephrine ki-

- netics in patients with essential hypertension. *Jpn Circ J* 47: 1232, 1983
8. SUZUKI H, KONDO K, SARUTA T: Effect of potassium chloride on blood pressure in two-kidney, one clip Goldblatt hypertensive rats. *Hypertension* 3: 566, 1981
 9. FUJITA T, SATO Y: Natriuretic and antihypertensive effects of potassium in DOCA-salt hypertensive rats. *Kidney Int* 24: 731, 1983
 10. MACGREGOR GA, SMITH SJ, MARKANDU ND, BANKS RA, SAGNELLA GA: Moderate potassium supplementation in essential hypertension. *Lancet* II: 567, 1982
 11. IIMURA O, KIJIMA T, KIKUCHI K, MIYAMI A, ANDO T, NAKAO T, TAKIGAMI Y: Studies on the hypotensive effect of high potassium intake in patients with essential hypertension. *Clin Sci* 61 (Suppl): 77s, 1981
 12. FUJITA T, ANDO K: Hemodynamic and endocrine changes associated with potassium supplementation in sodium-loaded hypertensives. *Hypertension* 6: 184, 1984
 13. MENEELY GR, BATTARBEE HD: High sodium-low potassium environment and hypertension. *Am J Cardiol* 38: 768, 1976
 14. EMMANUEL DA, SCOTT JB, HADDY SJ: The vasodilator action of potassium. *Am J Physiol* 197: 637, 1959
 15. CHEN WT, BRACE RA, SCOTT JB, ANDERSON DK, HADDY FJ: The mechanism of the vasodilator action of potassium. *Proc Soc Exp Biol Med* 140: 820, 1972
 16. WRIGHT FS, STRIEDER N, FOWLER NB, GIEBISCH G: Potassium secretion by the distal tubule after potassium adaptation. *Am J Physiol* 221: 437, 1971
 17. BRANDIS M, KEYES J, WINDHAGER EE: Potassium induced inhibition of proximal tubular fluid reabsorption in rats. *Am J Physiol* 222: 421, 1972
 18. YOUNG DB, MCCAA RE, PAN Y, GUYTON AC: The natriuretic and hypotensive effects of potassium. *Circ Res* 38 (Suppl II): II-84, 1976
 19. GOTO A, TOBIAN L, IWAI J: Potassium feeding reduces hyperactive central nervous system pressor responses in Dahl salt sensitive rats. *Hypertension* 3 (Suppl I): I-128, 1981
 20. VANDER AJ: Direct effects of potassium on renin secretion and renal function. *Am J Physiol* 219: 455, 1970
 21. BRUNNER HR, BAER L, SEALEY JE: The influence of potassium administration and deprivation on renin in normal hypertensive subjects. *J Clin Invest* 49: 2128, 1970
 22. MIURA Y, CAMPESE V, DeQUATTRO V, MEIJER D: Plasma catecholamines via an improved fluorimetric assay: Comparison with an enzymatic method. *J Lab Clin Med* 89: 421, 1977
 23. BUFANO G, VAONA G, STARCICH R: Approach to the pharmacokinetics of dl-7-³H-noradrenaline. *Eur J Clin Pharmacol* 6: 88, 1973
 24. GREENBLATT DJ, KOCH-WESER J: Drug therapy: Clinical pharmacokinetics. *N Engl J Med* 293: 702 and 964, 1975
 25. ENGELMAN K, PORTNOY B: A sensitive double isotope derivative assay for norepinephrine and epinephrine: Normal resting human plasma levels. *Circ Res* 26: 53, 1970
 26. DeQUATTRO V, MIURA Y: Neurogenic factors in human hypertension: Mechanism or myth? *Am J Med* 55: 362, 1973
 27. KOPIN IJ, LAKE RC, ZIEGLER M: Plasma levels of norepinephrine. *Ann Intern Med* 88: 671, 1978
 28. SILVERBERG AB, SHAH SD, HAYMOND MW, CRYER PE: Norepinephrine: hormone and neurotransmitter in man. *Am J Physiol* 234: E252, 1978
 29. ESLER M, JACKMAN G, BOBIK A, LEONARD P, KELLEHER D, SKEWS H, JENNINGS G, KORNER P: Norepinephrine kinetics in essential hypertension: Defective neuronal uptake of norepinephrine in some patients. *Hypertension* 3: 149, 1981
 30. MAAS JW: A kinetic model for the study of the disposition of circulating norepinephrine. *J Pharmacol Exp Ther* 174: 369, 1970
 31. GHIONE S, PALOMBO C, PELLEGRINI M, FOMMEI E, PILO A, DONATO L: The kinetics of plasma noradrenaline in normal and hypertensive subjects. *Clin Sci Mol Med* 55: 89s, 1978
 32. FITZGERALD GA, HOSSMANN V, HAMILTON CA, REID JL, DAVIES DS, DOLLERY CT: Inter-individual variation in kinetics of infused epinephrine. *Clin Pharmacol Ther* 26: 669, 1979
 33. ESLER M, JACKMAN G, BOBIK A, KELLEHER D, JENNINGS G, LEONARD P, SKEWS H, KORNER P: Determination of norepinephrine apparent release rate and clearance in humans. *Life Sci* 25: 1461, 1979
 34. FITZGERALD GA, BARNES P, HAMILTON CA, DOLLERY CT: Circulating adrenaline and blood pressure: The metabolic effects and kinetics of infused adrenaline in man. *Eur J Clin Invest* 10: 401, 1980
 35. RUBIN PC, SCOTT PJW, McLEAN K, REID JL: Noradrenaline release and clearance in relation to age and blood pressure in man. *Eur J Clin Invest* 12: 121, 1982
 36. GOLDSTEIN DS, HORWITZ D, KEISER HR, POLINSKY RJ, KOPIN IJ: Plasma l-[³H] norepinephrine, d-[¹⁴C] norepinephrine, and d,l-[³H] Isoproterenol kinetics in essential hypertension. *J Clin Invest* 72: 1748, 1983
 37. LANGER SZ, CAVERO I, MASSINGHAM R: Recent developments in noradrenergic neurotransmission and its relevance to the mechanism of action of certain antihypertensive agents. *Hypertension* 2: 372, 1980
 38. GROSSMAN SH, DAVIS D, GUNNELLS JC, SHAND DG: Plasma norepinephrine in the elevation of baroreceptor function in humans. *Hypertension* 4: 566, 1982
 39. CLUTTER WE, BIER DM, SHAM SD, CRYER PE: Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. *J Clin Invest* 66: 94, 1980
 40. CRYER PE, RIZZA RA, HAYMOND MW, GERICH JE: Epinephrine and norepinephrine are cleared through beta-adrenergic, but not alpha-adrenergic, mechanisms in man. *Metabolism* 29 (Suppl I): 1114, 1980

41. DIETZ R, SCHÖMIG A, RASCHER W, STRASSER R, GANTEN U, KUBLER W: Partial replacement of sodium by potassium in the diet restores impaired noradrenaline in activation and lowers blood pressure in stroke-prone spontaneously rats. *Clin Sci* 61: 69s, 1981
42. BOGDANSKI DF, BRODIE BB: The effects of inorganic ions on the storage and uptake of ^3H -norepinephrine by rat heart slices. *J Pharmacol Exp Ther* 165: 181, 1969
43. BOGDANSKI DF, BLASZKOWSKI TP, TISSARI AH: Mechanisms of biogenic amine transport and storage IV. Relationship between K and the Na requirement for transport and storage of 5-hydroxytryptamine and norepinephrine in synaptosomes. *Biochim Biophys Acta* 211: 521, 1970
44. BLAUSTEIN MP, HAMLYN JM: Role of a natriuretic factor in essential hypertension: An hypothesis. *Ann Intern Med* 98: 785, 1983
45. HADDY FJ: Sodium-potassium pump in low-renin hypertension. *Ann Intern Med* 98: 781, 1983
46. DE WARDENER HE, MACGREGOR GA, CLARKSON EM, ALAGHBAN-ZADEH J, BITENSKY LE, CHAYEN J: Effect of sodium intake on ability of human placenta to inhibit renal Na-K adenosine triphosphate in vitro. *Lancet* I: 411, 1981
47. SKRABAL F, AUBÖCK J, HORTNAGL H, BRAUNTEINER H: Effect of moderate salt restriction and high potassium intake on pressor hormones, response to noradrenaline and baroreceptor function in man. *Clin Sci* 59: 157s, 1980
48. WOOD AJJ, FELDMAN R, NADEAU J: Physiological regulation of beta-receptors in man. *Clin Exp Hypertension* A4: 807, 1982