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# High and Low Dietary Potassium Effects on Rat Vascular Sodium Pump Activity (42614)

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*Abstract.* Studies of renal and other tissues suggest that chronic elevation or reduction of dietary potassium intake could affect vascular smooth muscle sodium pump (Na-pump) activity. To examine this possibility, the effects of 3 weeks of low (LK; 4 mmole KCl/kg chow), normal (NK; 162 mmole/kg), and high (HK; 1350 mmole/kg) dietary potassium intake on Na-pump activity, the Na-pump activity response to changes in extracellular potassium concentration, and Na-pump site density were determined in tail arteries of rats. Plasma potassium concentration was elevated by 21% in HK rats and reduced by 45% in LK rats. When incubated in autologous plasma, compared to arteries from NK rats, Na-pump activity was decreased in the tail arteries from LK rats but not altered in those from HK rats. When arteries from NK and LK rats were incubated in autologous plasma with the potassium concentration increased to equal that of the HK rats, Na-pump activity exceeded that of HK rat arteries; Na-pump activity of arteries incubated in autologous plasma did not differ from that of arteries incubated in Krebs–Henseleit buffer with the potassium concentration adjusted to equal that of the plasma. Tail artery Na-pump activity for all three dietary potassium groups increased as potassium concentration of the incubation medium was increased from 1 to 12 m*M*; Na-pump activity was similar for the NK and LK rats at all potassium concentrations, but Na-pump activity of HK rat arteries was less than that of NK arteries at high extracellular potassium concentrations. Na-pump site density was not altered by either HK or LK diet. It is concluded that in tail arteries of rats fed the LK diet, chronically decreased extracellular potassium results in chronically decreased Na-pump activity. In contrast, an adaptive change occurs in tail arteries of rats fed HK diet, such that Na-pump activity remains at normal levels despite elevated extracellular potassium; this adaptive response to chronically increased dietary potassium does not appear to be the result of decreased Na-pump site density. 

Cardiovascular, renal, endocrine, and biochemical responses to chronic alterations of extracellular potassium concentration resulting from increased or decreased dietary potassium intake have been documented in a variety of experimental models (1–11). Acute changes in extracellular potassium concentration markedly alter vascular smooth muscle membrane potential and tension development (12), presumably as a result of altered vascular smooth muscle sodium pump (Na-pump) activity (13, 14). In addition, chronic hypokalemia and hyperkalemia have been shown to alter $Na^+$, $K^+$-ATPase, or Na-pump activity in human blood cells and many different animal tissues (15–20). The effects of chronic high potassium diet on renal function are well documented (6, 7, 19–22); the potassium adaptation response of kidney is characterized by increased excretion of an acute potassium load, changes in basolateral membrane, and increase in $Na^+$, $K^+$-ATPase activity (5–7, 19, 22). Effects of altered potassium diet in other tissues are less consistent; while chronic potassium deficiency resulted in a 130% increase in $Na^+$, $K^+$-ATPase activity in guinea pig heart muscle (4) and an increased number of ouabain-binding sites in human erythrocytes (16), opposite effects were reported for rat skeletal muscle and mesenteric arterioles, in which potassium depletion markedly decreased both Na-pump site density and Na-pump activity (18, 23).

Na-pump activity of vascular smooth muscle is an important variable in regulation of vascular function; it is well known that acute changes in vascular smooth muscle Na-pump activity, resulting from increased or decreased extracellular potassium concentration, alter vascular resistance to blood flow and contractile responses to vasoactive agents (8–12, 24–27). Thus, if chronically altered dietary potassium intake affects Na-



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pump activity in vascular smooth muscle as in the kidney, this could alter vascular smooth muscle function. To assess this possibility, the present study was conducted to determine the effect of chronic reduction and elevation of extracellular potassium on vascular smooth muscle Na-pump activity, using tail arteries of rats chronically fed a high or low potassium diet as an experimental model.

**Materials and Methods.** Effects of chronically altered dietary potassium intake were assessed in Wistar rats (Harlan Industries) housed in group cages in a temperature (24°C)- and humidity (50%)-controlled room, illuminated between 6:00 AM and 6:00 PM, with free access to tap water. Prior to being fed experimental diets, rats were fed standard rat chow (Purina 5001). During the 21-day experimental diet period, rats were fed either a low potassium diet (ICN Nutritional Biochemicals, Cleveland, OH) containing 4 mmol KCl/kg chow (LK group) or the same diet supplemented with either a normal (162 mmol KCl/kg diet; NK group) or a supranormal (1350 mmol KCl/kg diet; HK group) amount potassium. Rats were weighed weekly before and throughout the experimental period.

*Protocol 1.* At the end of the diet period, rats were anesthetized (chloral hydrate, 300 mg/kg, and xylazine, 10 mg/kg, ip) in sets of three, comprising one rat each from LK, NK, and HK groups. Tail arteries were removed, washed, and cut in segments for determination of Na-pump activity. Na-pump activity in tail arteries from HK, NK, and LK rats was determined during incubation in three incubation media: (a) autologous plasma; (b) autologous NK and LK rat plasma after addition of sufficient KCl to raise the potassium concentration to equal that of the HK rat in the set; and (c) Krebs–Henseleit buffer (millimolar concentrations: $NaHCO_3$, 27.2; NaCl, 117.0; $NaH_2PO_4 \cdot H_2O$, 1.0; $MgSO_4 \cdot H_2O$, 1.2; $CaCl_2 \cdot 2H_2O$, 2.5; dextrose, 11.0) with the potassium concentration adjusted to equal that of the HK rat in the set.

*Protocol 2.* At the end of the diet period, rats were anesthetized and tail arteries were removed; Na-pump activity was measured during incubation in Krebs–Henseleit buffer (composition as in Protocol 1) containing 1, 4, 12, or 24 m*M* KCl; osmolality of the incubation solutions was maintained constant by adjustment of NaCl concentration.

*Protocol 3.* At the end of the diet period, rats were anesthetized and tail arteries were removed for determination of Na-pump site density by measurement of [$^3$H]ouabain binding. The equilibrium dissociation constant, $K_d$, and the number of binding sites, $B_{max}$, were calculated from the equilibrium-binding data by Scatchard analysis.

*Determination of Na-pump activity.* Rubidium-86 uptake was measured to estimate vascular smooth muscle Na-pump activity, using a method similar to that described previously (28, 29). Following the 3-week diet period, rats were anesthetized, blood was collected in heparinized syringes (Sarstedt Co.) by aortic puncture, and the tail artery was removed and placed in Krebs–Henseleit buffer (composition as in Protocol 1 plus 5 m*M* KCl). The time elapsed between the blood collection and artery isolation never exceeded 2 min. Blood was centrifuged immediately in a refrigerated centrifuge (4°C for 10 min), and plasma was separated and kept in room temperature until the arteries were ready for the assay (ca. 10 min). Arteries were then cleaned in fresh Krebs solution and cut into several pieces of approximately 1 cm. This procedure was completed within 5 min at room temperature. The pieces of artery were then transferred into beakers containing ice-cold (4°C) $K^+$-free Krebs–Henseleit buffer for a 20-min preincubation. This procedure allows the tissue to accumulate sodium, thus maximizing subsequent Na-pump activity. It was determined in preliminary studies that a preincubation period of 10 min is sufficient to maximize the specific $^{86}Rb^+$ uptake in tail arteries. The segments were then transferred into incubation tubes containing 0.5 ml of plasma or Krebs–Henseleit buffer, with or without 1 mM ouabain, warmed up for 2 min, and the reaction was started by addition of $^{86}$RbCl (10–50 n*M*, $10^6$ cpm/ml). Incubation tubes were flushed with 95% $O_2$ + 5% $CO_2$ for 30 sec, without bubbling the incubation medium, and then stoppered and incubated while

gently shaking for 17 min at 37°C. The artery segments were then removed and rinsed four times in fresh Krebs–Henseleit buffer (composition as in Protocol 1 plus 5 m*M* KCl) at room temperature. This washing step was completed in 30 sec. They were then blotted dry, and placed in polyethylene tubes for determination of radioactivity by gamma counting (Beckman, Gamma 4000). Artery segments were then dried to constant weight, which averaged approximately 0.5 mg/segment.

Rubidium-86 uptake in the presence of 1 m*M* ouabain, considered to reflect distribution in extracellular spaces and passive penetration into cells, termed nonspecific uptake, constituted 15–25% of the total uptake and was not altered by the dietary treatments. Specific $^{86}Rb^+$ uptake, defined as the difference between $^{86}Rb^+$ uptake in the absence and in the presence of ouabain, is considered to reflect uptake by the Na-pump. Based on the finding that uptake of $Rb^+$ reflects simultaneous uptake of an amount of potassium that is proportionate to its concentration in the incubation medium (30), we expressed Na-pump activity as combined uptake of $^{86}Rb^+$ and potassium. Values are expressed as nmole ($^{86}Rb^+ + K^+$)/mg dry tissue/17 min of incubation. Rubidium-86 uptake was found to be linear up to 40 min under these conditions.

*Binding studies.* Sodium-pump site density in rat tail arteries were estimated by [$^3$H]ouabain binding to freshly isolated arteries (31–33). After removal, tail arteries were isolated, cleaned, cut into 1-cm sections, and placed in Krebs–Henseleit buffer, 37°C, pH 7.4 (composition as in Protocol 1) containing 5.0 m*M* KCl, gassed with 95% $O_2$–5% $CO_2$. Tail arteries from 10–15 rats per treatment group were pooled in this solution and equilibrated for 1 hr. After the equilibration period, groups of three artery pieces each were transferred into test tubes containing 0.5 ml of $K^+$-free Krebs solution and varying concentrations of [$^3$H]ouabain. Nonspecific binding in the presence of 0.1 m*M* unlabeled ouabain was determined for each [$^3$H]-ouabain concentration tested. Artery sections were incubated for 90 min; in preliminary time course experiments, equilibrium binding was achieved by 40 min and maintained through 90 min. At the end of the incubation period, the tissues were removed and rinsed for 2 sec in $K^+$- and tracer-free Krebs solution at room temperature. Two additional 5-min washes at 0°C followed for the removal of extracellular label. Tissues were then blotted and dried to constant weight. Dry weights were recorded, and tissues were dissolved in 0.2 ml NCS tissue solubilizer (Amersham) for at least 3 hr and neutralized with glacial acetic acid. Radioactivity in each tissue was determined in a scintillation counter after addition of 8 ml Biocount. Specific binding was determined as the difference in binding in the absence and presence of 0.1 m*M* unlabeled ouabain. The nonspecific binding ranged from 20 to 30% of the total binding. $K_d$ and $B_{max}$ for [$^3$H]ouabain binding were obtained from the equilibrium-binding data by Scatchard analysis. The $K_d$ value for the control group was verified earlier in another group of rats by kinetic studies.

*Statistical analysis.* Data are expressed as mean ± SE. Group mean values for different dietary treatments were compared using ANOVA followed by the Newman–Keuls test; a $P$ value of less than 0.05 was considered significant. Slopes of the Scatchard plots were determined by linear regression analysis.

**Results.** Plasma potassium concentration was reduced by 45% in LK rats and was elevated by 21% in the HK group. The effects of increased and decreased dietary potassium intake on basal tail artery Na-pump activity are shown in Table I. When incubated in autologous plasma, compared with arteries from rats fed the NK diet, Na-pump activity was not significantly altered in arteries from rats fed the HK diet but was decreased by 30% in arteries from rats fed the LK diet. When tail arteries were incubated in autologous plasma with the potassium concentration increased to equal that of the HK rat plasma, Na-pump activity was significantly greater in tail arteries from both NK and LK rats than in arteries from the HK rats. There was no difference, for any of the groups studied, between Na-pump activity of tail arteries incubated in autologous plasma and arteries

TABLE I. SODIUM-PUMP ACTIVITY (nmol/mg dry wt/17 min) OF TAIL ARTERIES OF RATS FED FOR 21 DAYS A DIET CONTAINING NORMAL (NK), LOW (LK) OR HIGH (HK) AMOUNTS OF POTASSIUM, INCUBATED IN THE RAT'S OWN PLASMA, WITH OR WITHOUT ADJUSTMENT OF POTASSIUM CONCENTRATION TO EQUAL THAT OF THE HK RAT PLASMA, OR IN KREBS SOLUTION WITH POTASSIUM CONCENTRATION EQUAL TO THAT OF THE HK RAT PLASMA

| Diet group | In autologous plasma | In autologous plasma ([K]adj) | In Krebs ([K]adj) |
|---|---|---|---|
| HK | 43.8 ± 3.5 | 43.8 ± 3.5* | 43.0 ± 4.0* |
| NK | 45.7 ± 5.4 | 59.9 ± 5.7§ | 60.3 ± 5.8§ |
| LK | 28.2 ± 2.3* | 55.9 ± 5.9§ | 59.1 ± 5.3§ |

*Note.* Values are expressed as means ± SE; *$P < 0.05$ vs NK group in same incubation medium; §$P < 0.05$ vs same dietary group in autologous plasma; $N = 9–10$ rats per diet group.

incubated in Krebs–Henseleit solution of equal potassium concentration. Nonspecific $^{86}Rb^+$ uptake, plasma sodium concentration, body weights, and hematocrit values did not differ among the diet groups (Table II).

Two observations suggested that, in rats fed a high potassium diet, there occurs an adaptive response that is characterized by suppression of the stimulatory effect of increased extracellular potassium concentration of vascular Na-pump activity. First, when arteries from NK- and HK-diet rats were incubated in autologous plasma, Na-pump activities were not different, despite the higher potassium concentration in the HK-diet rat plasma. And, second, when incubated at equal potassium concentration, in either autologous plasma or buffer, Na-pump activity was significantly lower in tail arteries from HK-diet rats than in those from either NK- or LK-diet rats. The results shown in Fig. 1 confirm this conclusion; although increasing the potassium concentration of the incubation medium increased Na-pump activity in tail arteries from all three dietary potassium groups, this effect was not as great for arteries from rats fed the HK diet as for those fed the LK or NK diets. As a result, at incubation medium KCl concentrations of 4 m*M* or more, Na-pump activity of tail arteries from rats fed the HK diet was significantly less than that of arteries from rats fed the NK diet or the LK diet. Tail artery Na-pump activity responses to changes in potassium concentration did not differ between the NK and the LK rats.

Ouabain-binding studies were carried out using tail arteries from rats fed the three potassium diets to assess whether the reduced stimulatory effect of increased extracellular potassium concentration was associated with Na-pump site down-regulation in rats fed the HK diet. Scatchard analysis of equilibrium binding resulted in a linear plot, suggesting a single population of [$^3$H]ouabain-binding sites in all treatment groups; nonspecific ouabain binding was 20–30% of total binding and did not vary significantly among the

TABLE II. EFFECT OF HIGH (HK), NORMAL (NK), AND LOW (LK) POTASSIUM DIET ON NONSPECIFIC UPTAKE, PLASMA $Na^+$ AND $K^+$ CONCENTRATIONS, BODY WEIGHT, AND HEMATOCRIT

| Measurement | HK | NK | LK |
|---|---|---|---|
| Nonspecific uptake (nmol/mg/17 min) | 7.96 ± 0.95 | 7.67 ± 0.83 | 6.01 ± 0.92 |
| Plasma [$K^+$] (mEq/liter) | 5.66 ± 0.31* | 4.68 ± 0.17 | 2.56 ± 0.17* |
| Plasma [$Na^+$] (mEq/liter) | 137 ± 2 | 138 ± 1 | 139 ± 2 |
| Body weight (g) | 348 ± 7 | 391 ± 17 | 351 ± 12 |
| Hematocrit (%) | 42 ± 1 | 40 ± 1 | 42 ± 1 |
| Number of rats | 9 | 10 | 10 |

* $P < 0.05$ compared to NK.

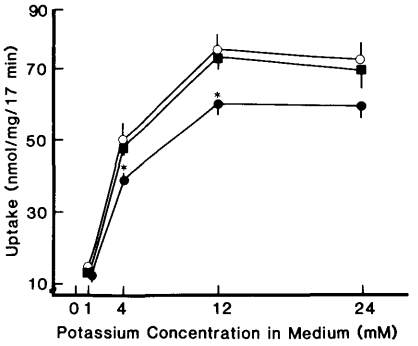


FIG. 1. Relationship between extracellular potassium concentration and vascular Na-pump activity in tail arteries from rats maintained for 21 days on high (solid circles), normal (solid squares) or low (open circles) dietary potassium intake. Values represent means ± SE for eight rats per dietary group. *$P < 0.05$ compared to normal potassium group values.

three groups. As shown in Table III, the density of specific ouabain-binding sites, expressed as fmole [$^3$H]ouabain bound/mg tissue, did not differ significantly between the rats fed the NK diet and those fed either the HK or the LK diet. There was, however, a significantly greater binding site density for the HK-diet rats compared with the LK-diet rats. $K_d$ values did not differ significantly among the three groups.

**Discussion.** Renal adaptation to chronic intake of high potassium is well documented. Kidney responds to a high potassium load by increasing its ability to excrete the excess potassium (5, 7, 22). This response is associated with an elevation of plasma aldosterone levels and with increased secretion of potassium in the collecting tubules (7, 22). A structural adaptation of the basolateral membrane cells and stimulation of $Na^+$, $K^+$-ATPase in the collecting tubules is also reported during high potassium intake (6, 7, 19). Effects of altered dietary potassium in other tissues are less well defined. The present study demonstrates that after 3 weeks of high dietary potassium (HK) intake, which resulted in elevated plasma potassium concentrations, rat tail artery Na-pump activity is altered, such that the stimulatory effect of elevated extracellular potassium concentration on the pump activity is diminished. In contrast, chronic exposure to reduced extracellular potassium resulting from a low potassium (LK) diet did not alter the relationship between potassium concentration and tail artery Na-pump activity. The mechanism responsible for this effect of increased dietary potassium cannot be fully defined, but, on the basis of the [$^3$H]-ouabain-binding study, down-regulation of Na-pump site density does not appear to be responsible for the diminished response to increased extracellular potassium. On the contrary, there was a tendency for specific ouabain-binding site density to be increased by the HK diet and decreased by the low potassium (LK) diet. Thus, neither the value for rats eating the HK diet nor the value for rats eating the LK diet differed significantly from the control value (NK diet); binding-site density was 30% greater for tail arteries from HK-diet rats than for those from LK-diet rats. Taking in combination the binding-site density and the Na-pump activity at equal incubation medium potassium concentration, the ratio of uptake to binding-site density for the HK-diet rat arteries was only about 60% of the values for the NK- or LK-diet rat arteries. Thus, the results of this study suggest that chronically increased dietary potassium intake resulted either in the emergence of nonfunctional, but specific, ouabain-binding sites, or in an increased population of Na-pump sites having a reduced turnover, or both.

There may be other factors influencing the pump activity during chronic treatment with

TABLE III. SODIUM-PUMP SITE DENSITY, $B_{max}$, AND DISSOCIATION CONSTANT, $K_d$; VALUES DETERMINED FROM [$^3$H]OUABAIN BINDING STUDIES IN TAIL ARTERIES FROM RATS FED HIGH (HK), NORMAL (NK), OR LOW (LK) DIETARY POTASSIUM

| Treatment | $B_{max}$ (fmol/mg dry wt) | $K_d$ (nM) | $N$ | $n$ |
|---|---|---|---|---|
| HK | 73 ± 8 ┐ | 36 ± 3 | 3 | 43 |
| NK | 61 ± 7 * | 39 ± 3 | 4 | 56 |
| LK | 56 ± 4 ┘ | 42 ± 6 | 4 | 58 |

*Note.* Data are presented as means ± SE; $N$ represents number of experiments; $n$ represents number of rats used for each $N$; *$P = 0.05$.

high or low potassium. Aldosterone is known to stimulate $Na^+$, $K^+$-ATPase activity in kidney and in other tissues (34–37). Although plasma aldosterone levels were not measured in this study, based on similar studies by other investigators, it is reasonable to assume that aldosterone was increased in the plasma of HK rats in this study. In the kidney, Mujais *et al.* (37) have shown that chronic infusion of aldosterone, which mimics the high physiologic levels obtained during potassium loading, produces a time-dependent increase in $Na^+$, $K^+$-ATPase activity in the cortical collecting tubule in both rats and rabbits. This increase in enzyme activity was accompanied by a parallel increase in specific [$^3$H]ouabain binding in aldosterone-treated rabbits, indicating an increase in the number of enzyme units, since affinity of the enzyme for either $Na^+$ or $K^+$ was unaltered. However, potassium per se may also have an effect on activity of $Na^+$, $K^+$-ATPase independent of aldosterone. For example, Garg and Narang (21) have demonstrated that $Na^+$, $K^+$-ATPase activity increases with increased diet potassium in the cortical collecting duct in adrenalectomized rabbits. This increase in enzyme activity was accompanied by an increase in potassium excretion. A chronic potassium diet also stimulates $Na^+$, $K^+$-ATPase activity in the homogenized renal cortex, medulla, and in the collecting tubules of mice and rats (19, 20), an effect also independent of aldosterone. This increase appears to be specific to the renal tissue, as brain, liver and the skeletal muscle enzymes are unaffected (20).

Aldosterone is also known to stimulate $Na^+$ transport (34), $K^+$ turnover (35) and, more specifically, ouabain-sensitive $Na^+$-efflux, the Na-pump (36) in arterial smooth muscle in *in vitro* preparations. Although we did not measure plasma levels of aldosterone in this study, exposure to plasma aldosterone or other substances which may have been altered during potassium diet does not appear to be important for our conclusions, since comparison of adjusted plasma and Krebs did not reveal any differences in vascular Na-pump activity. It should also be pointed out that in the present study, as in most studies of this type, total osmolar intake and thus water turnover varies directly with potassium content of the diet (5). It was shown earlier in this laboratory that 13-day treatment with HK diet resulted in a doubling of the fluid intake and urine volume (5). The contribution of these nonspecific alterations in fluid and osmolar contents has not been assessed.

Other studies have demonstrated varied and contrasting alterations in Na-pump activity, specific binding of [$^3$H]ouabain or site density, or $Na^+$, $K^+$-ATPase activity in a variety of tissue and cell systems following chronic exposure to increased or decreased extracellular potassium. In the present study we have demonstrated an apparent dissociation between the effect on the number of binding sites and the rate of Na-pump activity. In an earlier study, Erdmann *et al.* (4) found that chronic potassium deficiency for 10–18 days results in a 130% increase in $Na^+$, $K^+$-ATPase activity in quinea pig heart muscle. There was no change in kinetic properties of the enzyme, suggesting that the increase was due to an increase in the number of enzyme units. In contrast, Nørgaard *et al.* (23) have shown that potassium depletion markedly decreases both Na-pump site density and Na-pump activity in rat skeletal muscle. The nature of these two tissues, skeletal vs heart muscle, may explain the discrepancies between the two studies. Skeletal muscle has the largest depot of potassium in the body. During potassium depletion it loses potassium and gains sodium. By contrast, the sodium and potassium contents of other organs (38–40), including the heart (16), remain constant for several weeks. In the vascular tissue, Aalkajær *et al.* (18) determined Na-pump site numbers in rat mesenteric arteriols. Three weeks of potassium depletion produced at 35% reduction of specific [$^3$H]ouabain-binding sites. The principal difference between our study and Aalkajær's is that they used resistance vessels, whereas we used the tail artery which is considered a conduit artery. The second difference is the content of potassium in the LK diets; they used a diet lower in potassium (0.75 mmole K/kg) than we did (4 mmole K/kg). The binding methods used were also slightly different. Although both studies uti-

lized the whole tissue [$^3$H]ouabain binding, we analyzed our data using Scatchard transformation, a more widely accepted approach to receptor-binding studies. These differences may partly explain the conflicting results.

In conclusion, the results of this study suggest that an adaptive change occurs in the vascular smooth muscle Na-pump in rats chronically fed a high potassium diet. As a result of this change, Na-pump activity remains at normal levels despite increased extracellular potassium concentration. In contrast, in rats fed a potassium-deficient diet, chronically decreased extracellular potassium concentration is associated with decreased vascular Na-pump activity, a response consistent with that produced by acutely decreased potassium concentration. Further studies will be required to elucidate the mechanism responsible for the altered relationship between vascular Na-pump activity and extracellular potassium concentration in rats fed excess potassium, and to determine what changes, if any, in vascular smooth muscle function are associated with the chronically decreased Na-pump activity in potassium-deprived rats.

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1. Skrabal F, Auböck J, Hörtnagl H, Braunsteiner 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-160s, 1980.
2. Paller MS, Douglas JG, Linas SL. Mechanism of decreased vascular reactivity to angiotensin II in conscious, potassium-deficient rats. J Clin Invest **73**:79–86, 1984.
3. Workman ML, Paller MS. Cardiovascular and endocrine effects of potassium in spontaneously hypertensive rats. Amer J Physiol **249**:H907–H913, 1985.
4. Erdmann E, Bolte HD, Lüderitz B. The ($Na^+$ + $K^+$)-ATPase activity of guinea pig heart muscle in potassium deficiency. Arch Biochem Biophys **145**:121–125, 1971.
5. Nasjletti A, Erman A, Cagen LM, Brooks DP, Crofton JT, Share L, Baer PG. High potassium intake selectively increases urinary $PGF_{2\alpha}$ excretion in the rat. Amer J Physiol **248**:F382–F388, 1985.
6. Stanton B, Pan L, Deetjen H, Guckian V, Geibisch G. Independent effects of aldosterone and potassium of induction of potassium adaptation in rat kidney. J Clin Invest **79**:198–206, 1987.
7. Silva P, Brown RS, Epstein FH. Adaptation to potassium. Kidney Int **11**:466–475, 1977.
8. Chen W-T, Brace RA, Scott JB, Anderson DK, Haddy FJ. The mechanism of the vasodilator action of potassium. Pro Soc Exp Biol Med **140**:820–824, 1972.
9. Scott J, Emanuel D, Haddy F. Effect of potassium of renal vascular resistance and urine flow rate. Amer J Physiol **197**:305–308, 1959.
10. Emanuel DA, Scott JB, Haddy FJ. Effect of potassium on small and large blood vessels of the dog forelimb. Amer J Physiol **197**:637–642, 1959.
11. Anderson DK, Roth SA, Brace RA, Radawski D, Haddy FJ, Scott JB. Effect of hypokalemia hypomagnesemia produced by hemodialysis on vascular resistance in canine skeletal muscle. Circ Res **31**:165–173, 1972.
12. Hendrickx H, Casteels R. Electrogenic sodium pump in arterial smooth muscle cells. Pflügers Arch **346**:299–306, 1974.
13. Skou JC. The ($Na^+$ + $K^+$) activated enzyme system and its relationship to transport of sodium and potassium. Quart Rev Biophys **7**:401–434, 1975.
14. Fleming WW. The electrogenic $Na^+$, $K^+$-pump in smooth muscle: Physiologic and pharmacologic significance. Annu Rev Pharmacol Toxicol **20**:129–149, 1980.
15. Bluschke V, Bonn R, Greeff K. Increase in the ($Na^+$ + $K^+$)-ATPase activity in heart muscle after chronic treatment with digitoxin or potassium deficient diet. Eur J Pharmacol **37**:189–191, 1976.
16. Erdmann E, Kraweitz W. Increased number of ouabain binding sites in human erythrocyte membranes in chronic hypokalaemia. Acta Biol Med Germ **36**:879–883, 1977.
17. Duhm J, Göbel BO. $Na^+$-$K^+$ transport and volume of rat erythrocytes under dietary $K^+$ deficiency. Amer J Physiol **246**:C20–C29, 1984.
18. Aalkjær C, Kjeldsen K, Nørgaard A, Clausen T, Mulvany MJ. Ouabain binding and $Na^+$ content in resistance vessels and skeletal muscles of spontaneously hypertensive rats and $K^+$-depleted rats. Hypertension **7**:277–286, 1985.
19. Doucet A, Katz AI. Renal potassium adapation: Na-K-ATPase activity along the nephron after chronic potassium loading. Amer J Physiol **238**:F380–F386, 1980.
20. Silva P, Hayslett JP, Epstein FH. The role of Na-K-activated adenosine triphosphatase in potassium adaptation. J Clin Invest **52**:2665–2671, 1973.

21. Garg LC, Narang N. Renal adaptation in the adrenalectomized rabbit. J Clin Invest **76**:1065–1070, 1985.
22. Stanton BA, Giebisch GH. Potassium transport by the renal distal tubule: Effect of potassium loading. Amer J Physiol **243**:F487–F493, 1982.
23. Nørgaard A, Kjeldsen K, Clausen T. Potassium depletion decreases the number of $^3$H-ouabain binding sites and the active Na-K transport in skeletal muscle. Nature (London) **293**:739–741, 1981.
24. Bohr DF, Seidel C, Sobieski J. Possible role of sodium-calcium pumps in tension development of vascular smooth muscle. Microvasc Res **1**:335–343, 1969.
25. Day MD, Moore AF. Interaction of angiotensin II with noradrenaline and other spasmogens on rabbit isolated aortic strips. Arch Int Pharmacodyn Ther **219**:29–44, 1976.
26. Overbeck HW, Derifield RS, Pamnani MB, Sözen T. Attenuated vasodilator responses to K+ in essential hypertensive men. J Clin Invest **53**:678–686, 1974.
27. Overbeck HW, Clark DWJ. Vasodilator responses to $K^+$ in genetic hypertensive and in renal hypertensive rats. J Lab Clin Med **86**:973–983, 1975.
28. Songu-Mize E, Bealer SL, Caldwell RW. Phasic vascular sodium pump changes in deoxycorticosterone-hypertensive rats. Circ Res **55**:304–308, 1984.
29. Songu-Mize E, Bealer SL, Caldwell RW. Effect of DOCA-salt treatment duration and anteroventral third ventricle lesions on plasma-borne sodium pump inhibitor in rats. J Hypertension **5**:461–467, 1987.
30. Smith JM, Sanchez AA, Jones AW. Comparison of rubidium-86 and potassium-42 fluxes in rat aorta. Blood Vess **23**:297–309, 1986.
31. Brading A, Widdicombe JH. An estimate of sodium/potassium pump activity and the number of pump sites in the smooth muscle of the quinea-pig taenia coli, using [$^3$H]-ouabain. J Physiol London **238**:235–249, 1974.
32. Deth RC, Lynch CJ. The binding of $^3$H-ouabain to $Na^+$-$K^+$ATPase sites in arterial smooth muscle. Pharmacology **21**:29–37, 1980.
33. Wong SK, Westfall DP, Menear D, Fleming WW. Sodium-potassium pump sites, as assessed by [$^3$H]-ouabain binding, in aorta and caudal artery of normotensive and spontaneously hypertensive rats. Blood Vess **21**:211–222, 1984.
34. Friedman SM. Evidence for an enhanced transmembrane sodium ($Na^+$) gradient induced by aldosterone in the incubated rat tail artery. Hypertension **4**:230–237, 1982.
35. Garwitz ET, Jones AW. Aldosterone infusion into the rat and dose-dependent changes in blood pressure and arterial ionic transport. Hypertension **4**:374–381, 1982.
36. Moura AM, Worcel M. Direct action of aldosterone on transmembrane $^{22}$Na efflux from arterial smooth muscle. Hypertension **6**:425–430, 1984.
37. Mujais SK, Chekal MA, Jones WJ, Hayslett JP, Katz AI. Modulation of renal sodium-potassium-adenosine triphosphatase by aldosterone. J Clin Invest **76**:170–176, 1985.
38. Heppel LA. The electrolytes of muscle and liver in potassium-depleted rats. Amer J Physiol **127**:385–392, 1939.
39. Bradbury MWB, Kleeman CR. Stability of the potassium content of cerebrospinal fluid and brain. Amer J Physiol **213**:519–528, 1967.
40. Nattie EE. Brain tissue potassium in normal and potassium depleted rats. Life Sci **21**:1851–1856, 1977.

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