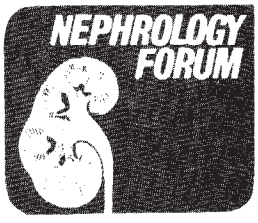
Sidney International, Vol. 30 (1986), pp. 116–127

NEPHROLOGY FORUM

Extrarenal potassium homeostasis

Principal discussant: ROBERT S. BROWN

Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts



Case presentation

A 35-year-old white woman came to the hospital complaining of severe weakness of several days duration. She had a 20-year history of anorexia nervosa, recently eating only cheese, unsalted crackers, chicken soup, and dilute lemon juice. For the past several years, she had taken 2 Ex-lax tablets per day and she excreted one soft bowel movement daily. She noted urinary frequency with polyuria, nocturia, and polydipsia; she drank approximately 12 glasses of fluid per day. She was in her usual state of health until one week prior to admission when she fell twice on ice. Over the week, she had moderate amounts of watery diarrhea, walked more slowly, and had difficulty climbing stairs. On the morning of admission, she collapsed on the floor, could not get up unaided, and was unable to dress herself.

The medical history was positive only for amenorrhea for the past 12 years. She had never been hospitalized or sought psychiatric evaluation and had not seen a physician for more than 4 years.

Physical examination revealed a blood pressure of 100/60 mm Hg; pulse, 80/min; respiratory rate, 22/min; temperature, 98.6° F; and weight, 37.7 kg. There were no orthostatic changes and she appeared euvolemic. The only abnormal finding was proximal muscle weakness of both arms and legs greater than expected for her poor nutritional status.

Laboratory studies showed a hematocrit of 40%; white blood cell count, 11,400 mm^3 with a normal differential; BUN, 21 mg/dl; creatinine, 0.7 mg/dl; and glucose, 88 mg/dl. The sodium was 141; potassium, 1.6; and chloride, 100 mEq/liter. The bicarbonate was 29 mmol/liter; calcium, 9.4 mg/dl; phosphate, 2.4 mg/dl; magnesium, 2.2 mEq/liter; and creatine phosphokinase (CPK), 798 U. Urinalysis had a specific gravity of 1.001; pH, 7.0; and negative protein and sediment. The electrocardiogram showed flattened T waves and prominent U waves. Within the first few hours of admission, urinary electrolytes on a random specimen had a sodium concentration of 33 mEq/liter; potassium, 7 mEq/liter; chloride, 63 mEq/liter; and bicarbonate, 0 mEq/liter. An arterial blood gas had a PO_2 of 78 mm Hg; PCO_2, 34 mm Hg; and pH, 7.46.

Figure 1 shows the initial potassium replacement and serum potassium levels. After she received 20 mEq of intravenous and 280 mEq of oral potassium chloride over 6 hours, the serum potassium had risen only to 2.1 mEq/liter. However, when an additional 60 mEq of intravenous and 180 mEq of oral potassium chloride was given over the next 5 hours, she complained of tingling sensations and muscle twitching. Chvostek's and Trousseau's signs were positive. She was treated with 2 g calcium chloride and 1 g magnesium chloride intravenously. Repeated blood studies and arterial blood gas levels were substantially unchanged, except for the serum potassium, which was now 8.3 mEq/liter, and the CPK, which was 2400 with 7% MB isoenzyme. An electrocardiogram showed peaked T waves over the precordium. After the hyperkalemia was discovered, 50 mEq sodium bicarbonate, 10 units crystalline zinc insulin, and 50 ml 50% dextrose were given intravenously. By 4 hours later, the serum potassium had fallen to 4.0 mEq/liter; symptoms and electrocardiographic abnormalities had resolved. The CPK returned to normal over the next several days, and all chemistries remained normal.

Discussion

DR. ROBERT S. BROWN (*Clinical Chief, Renal Unit, and Associate Physician, Beth Israel Hospital, and Associate Professor of Medicine, Harvard Medical School, Boston, Massachusetts*): This unusual 35–year-old woman presented with severe hypokalemia caused by the concurrence of a low potassium intake due to anorexia nervosa and an increased fecal potassium loss due to chronic laxative abuse. Urinary electrolyte measurements confirmed that renal potassium conservation was normal. She exhibited many of the findings seen with hypokalemia, including the polyuria and polydipsia associated with defective renal concentrating ability, muscle weakness, rhabdomyolysis, and electrocardiographic abnormalities. The house staff gave vigorous potassium replacement, and within 12 hours she developed tetany and life-threatening hyperkalemia. The experience with this patient poses several questions for us.

Presentation of the Forum is made possible by grants from Sandoz, Incorporated; Merck Sharp & Dohme; and E.I. du Pont de Nemours & Company.

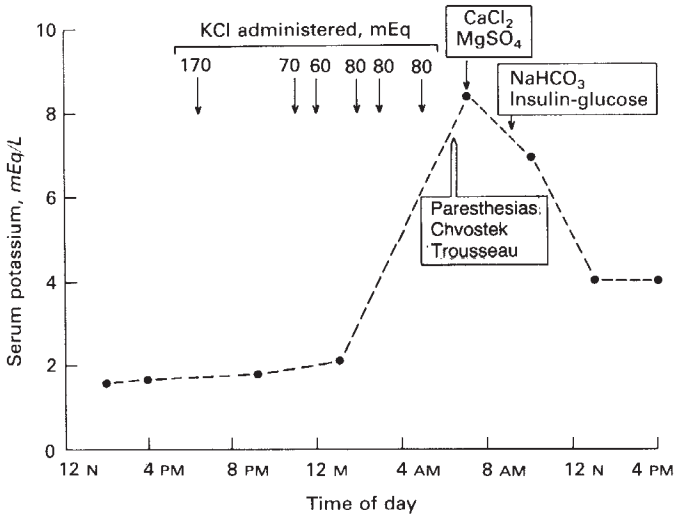


Fig. 1. *The patient's serum potassium concentration over the first 28 hours of hospitalization.* The doses and times (arrows) of potassium chloride administered, development of symptoms, and other therapies are shown (see text).

First, why did the first 300 mEq of potassium chloride cause only a minimal rise in the serum potassium, from 1.6 to 2.1 mEq/liter? Second, why did an additional load of only 240 mEq cause her serum potassium to rise to 8.3 mEq/liter? Third, why did she develop the symptoms of tingling sensations, muscle twitching, and tetany? I will defer these questions to review extrarenal potassium physiology and then attempt to answer them along the way.

Potassium distribution and cellular uptake

The potassium intake in a typical diet ranges from about 60 to 100 mEq/day. Less than 10% of this amount is excreted in the stool and, assuming sweat losses are small, most of the potassium is excreted in the urine. The kidney, in fact, serves as the regulatory organ for total body potassium balance over time. The extracellular fluid contains only 50 to 65 mEq, or less than 2%, of the total body exchangeable potassium stores. It therefore is not uncommon for many animals and humans to eat as much potassium in a single meal as that contained in the entire extracellular fluid. A potassium load is quickly absorbed from the gastrointestinal tract but only slowly excreted by the kidney (often less than one-half of such a potassium load is excreted in 4 to 6 hours), so the protection against hyperkalemia rests on the distribution of potassium between the intracellular and extracellular fluid compartments. Most of the approximately 3500 mEq of total exchangeable potassium in the body is within muscle cells, with lesser amounts in the liver and red blood cells.

To explain the high potassium concentration within cells, the membrane theory assumes first, that there are differential ion permeabilities through the cell membrane that can generate electrical potentials, and second, that the sodium pump actively maintains ion gradients and an electrical potential difference across the cell membrane. Using average values for the concentrations of sodium, potassium, and chloride inside muscle cells and in the extracellular fluid, the Nernst equation can be used to calculate the equilibrium potential for each ion (Table 1). As noted in Table 1, the calculated diffusion potentials of −97 mV for potassium and chloride are quite close to the actual measured value of about −90 mV for skeletal muscle cells [1]. Therefore, the high intracellular potassium and low intracellular chloride levels are to be expected by diffusion of these ions toward their equilibrium concentrations, which are dictated by the negative electrical potential inside the cell. The fact that the low intracellular and high extracellular sodium concentrations yield a calculated equilibrium potential (Table 1) far from the measured potential is consistent with active sodium transport against an electrochemical gradient. The electrogenic sodium pump responsible for sodium transport is sodium-potassium ATPase bound in the cell membrane. This pump extrudes 3 sodium ions from the cell in exchange for 2 potassium ions. Therefore, cellular potassium concentration depends mainly on the activity of sodium-potassium ATPase and on regulation of the cell membrane permeabilities to sodium and potassium ion. Together these two factors determine both the electronegative potential of the cell—so crucial to the function of excitable tissues such as nerves, heart, and skeletal muscle—and the uptake of potassium into the cell, an important determinant of cell volume and osmolality.

Table 1. Sodium, potassium, and chloride concentrations in intracellular fluid (ICF) and extracellular fluid (ECF) with the calculated diffusion potential of each ion (E_{ion})[a]

	Sodium	Potassium	Chloride
ICF	15 mEq/liter	150 mEq/liter	3 mEq/liter
ECF	150 mEq/liter[b]	4 mEq/liter	115 mEq/liter[b]
E_{ion}	+62 mV	−97 mV	−97 mV

[a] From Ref. 1.
[b] Corrected for Donnan factors.

Figure 2 shows an action potential of skeletal muscle with a normal resting potential of −90 mV. In hypokalemia, the cell is hyperpolarized, with a potassium concentration in the extracellular fluid that has decreased relatively more than that in the intracellular fluid. The increased electronegativity results in a larger gap between the resting potential and the threshold potential at which an action potential is propagated; this gap presumably accounts for the muscle weakness and eventual flaccid paralysis that occur with severe hypokalemia. The reverse situation occurs in hyperkalemia, in which the extracellular potassium concentration has increased relatively more than that in the cell, with a depolarized resting potential that is closer to the threshold potential. It seems likely that this phenomenon also occurs during the rapid replacement of potassium in extremely hypokalemic patients. In this situation, the rise of extracellular potassium is faster than that in the potassium-depleted cells and may be associated with a narrow gap between the resting and threshold potentials analogous to that of patients with hyperkalemia. The approximation of the resting potential to the threshold potential, in a manner similar to that in patients with hypocalcemia (which causes the threshold potential to approach the resting potential), accounts for the tetany and the positive Chvostek's and Trousseau's signs that are well described in patients receiving potassium replacement [2]. It is not uncommon for these findings to be transiently misdiagnosed as indicative of hypocalcemia or hypomagnese-

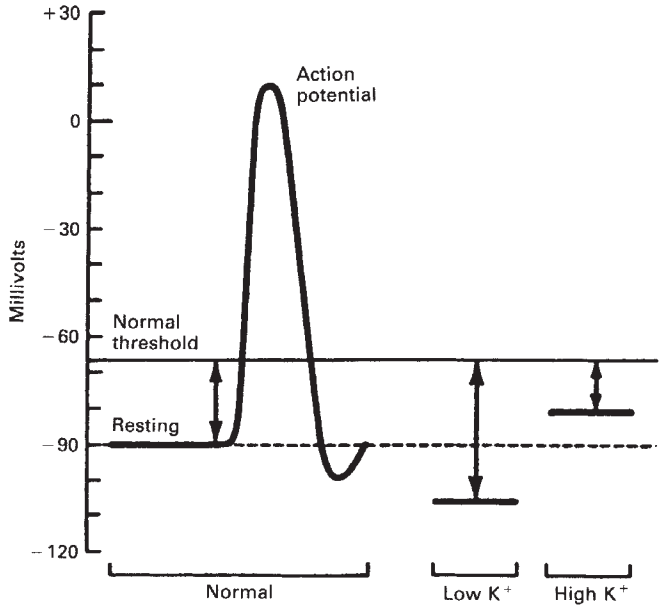


Fig. 2. *The electrical action potential of skeletal muscle and effect of potassium balance.* The solid horizontal line delineates the normal threshold potential of depolarization required to propagate an action potential; the broken line shows the resting potential when potassium balance is normal. In the potassium-depleted state, the resting potential is more negative (relatively hyperpolarized), whereas in hyperkalemia, the resting potential is less negative (relatively depolarized).

mia. That is in fact what occurred in this patient before the hyperkalemia was recognized.

Determinants of extrarenal potassium metabolism

When potassium loads that have the potential of doubling or tripling the extracellular potassium content are ingested, the avoidance of potassium intoxication depends on extrarenal as well as renal mechanisms [3]. It has been recognized for many years that adaptation to potassium loads that would take many hours to excrete is accomplished by the rapid distribution of potassium out of the extracellular fluid by cellular uptake. Alexander and Levinsky gave potassium loads to rats that had been adapted to a high-potassium diet and that had undergone bilateral nephrectomy; the plasma potassium concentration increased much less in these animals than in rats that previously had been eating a normal potassium diet [4]. Recent evidence has helped to delineate several mechanisms that modulate cellular potassium uptake and that might participate in the adaptive process of extrarenal tolerance to potassium loads. At least four factors, namely acid-base status, insulin, mineralocorticoids, and adrenergic activity, affect the relative distribution of total body potassium between the intracellular and extracellular fluids.

Effect of acid-base balance. The ability of acid-base balance to modulate potassium concentration is well recognized. Acidosis increases the plasma potassium by inducing a shift of potassium from the intracellular to the extracellular fluid, in addition to decreasing distal tubular potassium secretion by the kidney. Alkalosis decreases the plasma potassium by the opposite extrarenal and renal actions. It was a common rule of thumb that the potassium level would rise approximately 0.5 mEq/liter for each 0.1 fall in blood pH in acidosis [5]. However, as outlined by Adrogué and Madias and by Perez and colleagues, the relationship between pH and potassium changes is now known to be more complex and less predictable, with several other factors modulating the response of the plasma potassium to a given change in pH [6, 7] (Table 2). Acidosis usually causes a rise in the potassium level that is greater than the comparable fall in potassium that occurs with alkalosis [6]. Furthermore, metabolic disorders affect the plasma potassium considerably more than do respiratory ones [6, 8]. Bicarbonate may play a special role, because a fall in the plasma bicarbonate produces a significant rise in the plasma potassium, even if a decrease in the PCO_2 keeps the pH relatively constant [9]. The opposite effect is useful clinically: bicarbonate administration lowers potassium levels in patients with hyperkalemia even if the pH is unaffected [10].

Table 2. Factors modifying the extrarenal effect of acid-base changes on the plasma potassium

Modulating Factor	Greater $-\Delta K^+/\Delta pH$	Less $-\Delta K^+/\Delta pH$
1. Direction of pH change	Acidosis	Alkalosis
2. Origin of disorder	Metabolic	Respiratory
3. Determinant of plasma acidity changed	Bicarbonate	PCO_2
4. Nature of anion	Mineral acid	Organic acid
5. Duration of acidosis	Hours	Minutes

Mineral acids produce a larger rise in the plasma potassium concentration than do organic acids [6, 11–15], presumably because nonionized organic acids can enter the cell without causing a reciprocal movement of potassium or sodium outwards (as when a cationic proton enters a cell without chloride). Moreover, when an acid load is given, the pH changes most initially, but the rise in potassium lags until later [7, 16, 17], when the hydrogen ion has entered the cells, causing potassium to exit.

Effect of insulin. Insulin infusions decrease the plasma potassium by enhancing cellular uptake without producing an increment in renal potassium excretion [3, 18–21]. When potassium loads are large enough to raise the plasma concentration by at least 1 mEq/liter, insulin secretion is stimulated in dogs [19–22] and in humans [23], thus increasing cellular potassium uptake to correct hyperkalemia. But with more modest potassium loads that don't elevate the plasma insulin, the reduction of basal insulin by somatostatin infusion produces an increased plasma potassium without decreasing the amount of potassium excreted in the urine [24]. Cellular uptake of potassium can be restored to normal by restoration of basal insulin levels [24]; thus the basal level of insulin appears to be essential to potassium homeostasis. Cellular uptake of potassium, when stimulated by insulin, is initially predominant in splanchnic tissues, mainly the liver, and subsequently in peripheral tissues, mainly muscle [25]. In both tissues, potassium uptake is independent of insulin-stimulated glucose uptake [18, 25, 26]. This point is important to remember when using glucose and insulin in the treatment of hyperkalemia. Glucose should not be given alone, because if insulin secretion fails, as in a patient with

unrecognized diabetes, the resultant hyperglycemia and hyperosmolality will cause an extracellular shift of water and potassium and will exacerbate the hyperkalemia [18, 27–29]. Insulin's ability to augment potassium uptake in cell membranes appears to be the consequence of stimulation of the activity of sodium-potassium ATPase and hyperpolarization of the cell by a mechanism independent of cyclic AMP [30]. An additional insulin effect to stimulate sodium-hydrogen exchange across the cell membrane [31] may also augment potassium influx secondarily due to the decreased intracellular hydrogen ion.

Effect of mineralocorticoids. Although mineralocorticoids have a potent kaliuretic action, the magnitude of their role in extrarenal potassium metabolism is less well defined. It is well known that potassium loading and hyperkalemia stimulate aldosterone secretion by the adrenal zona glomerulosa [32, 33]. When a potassium load was given to anephric rats that had been adapted to a high-potassium diet, the augmented uptake of potassium by extrarenal tissues could be abolished by prior adrenalectomy and could be reproduced without a high-potassium diet by the administration of exogenous mineralocorticoids [4]. However, to obtain this effect, the mineralocorticoid had to be given prior to bilateral nephrectomy, and the dose used was many times that needed for physiologic replacement [4]. Aldosterone replacement in doses close to physiologic levels restored potassium tolerance toward normal in glucocorticoid-replaced, adrenalectomized rats receiving a potassium load after bilateral nephrectomy [34]. Aldosterone replacement also caused redistribution of potassium from the extracellular to the intracellular compartment, and reduced total exchangeable potassium in adrenalectomized dogs [35]. Mineralocorticoid administration corrects hyperkalemia in patients with hyporeninemic hypoaldosteronism without producing a detectable increase in renal or fecal potassium excretion [36] and in anuric dialysis patients [37]. The tissue site of this extrarenal effect of mineralocorticoids remains unclear; unfortunately, studies of the role of aldosterone in potassium transport by muscle both in vivo and in vitro have yielded conflicting results [18]. It is clear, however, that mineralocorticoids have an important effect on the colon: specifically, they increase potassium and decrease sodium content in the feces [38, 39]. This effect on potassium and sodium transport appears to be facilitated by an increase in potential difference across the colonic epithelium and by an increase in sodium-potassium ATPase activity [40, 41]. Glucocorticoids have effects on the colon similar to those of mineralocorticoids [38, 41], but these agents do not correct the defect in extrarenal potassium disposal caused by adrenalectomy, as do mineralocorticoids [34]. The mineralocorticoid action is initiated by binding to high-affinity cytosolic receptors for aldosterone, so-called type-I receptors, in contrast to the type-II receptors for the glucocorticoid hormones [42]; type-I receptors have been found in colon [43], hippocampus [44], mammary gland [45], and mononuclear leukocytes [46], in addition to the kidney [47]. Mineralocorticoids also increase potassium and decrease sodium concentrations in saliva [48, 49] and sweat [50]. In the absence of excessive sweating or diarrhea, however, the total amount of potassium excreted via these routes usually is not large enough to play an important role in overall potassium homeostasis.

Effect of adrenergic activity. Adrenergic activity does play an important role in potassium distribution. When Silva and Spokes induced chemical sympathectomy by injection of 6-hydroxydopamine in nephrectomized and adrenalectomized rats, the cellular uptake of a potassium load was significantly impaired and caused a greater degree of hyperkalemia [51]. This impairment of potassium tolerance was additive to the defect caused by streptozotocin-induced insulin deficiency and was corrected by epinephrine infusion [51]. We have extended these observations to humans. When healthy subjects were infused with a potassium load (Fig. 3), the simultaneous administration of propranolol significantly increased the serum potassium level and prolonged its elevation without changing urinary potassium excretion [52]. Moreover, when epinephrine was infused with the potassium load, the rise in serum potassium was markedly blunted (Fig. 4), whereas urinary potassium excretion decreased [52]. Changes in plasma aldosterone or insulin did not account for these findings; thus, it would appear that beta-adrenergic stimulation increases, and beta-blockade impairs, extrarenal disposal of a potassium load. Similar findings have been described by other investigators in animals [53–59] and in humans [60, 61].

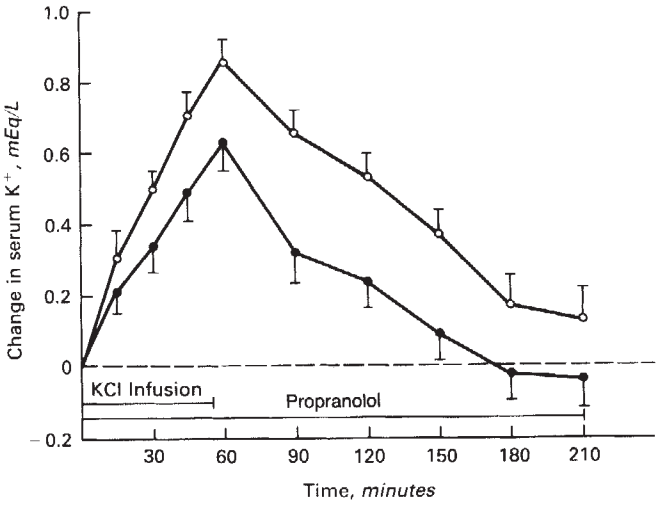


Fig. 3. *Effect of propranolol on the increment in serum potassium induced by an intravenous potassium load.* Changes in serum potassium with potassium loading are denoted by solid circles in the absence of propranolol and by open circles in the presence of propranolol. Values plotted indicate mean ± SEM in 9 subjects. The probability of the difference between treatments was <0.001 by repeated measure analysis. (Reproduced, by permission of the *New England Journal of Medicine* [302:431, 1980].)

The increased cellular uptake promoted by epinephrine appears to be a $beta_2$-specific effect, because it is duplicated by $beta_2$ agonists but not by $beta_1$ agonists [53, 55, 62, 63] and is blocked by $beta_2$-selective or nonselective beta antagonists [51, 55, 61, 63–65] but not by $beta_1$-selective antagonists [55, 63] or alpha antagonists [51, 53, 55, 59]. In contrast to the beta-adrenergic effect of increasing potassium tolerance via cellular uptake, alpha-adrenergic stimulation has the opposite effect. When the alpha-agonist phenylephrine was infused with a potassium load in healthy human subjects (Fig. 5), the rise in serum potassium was significantly augmented and prolonged, despite no change in urinary potassium excretion [66]. Furthermore, the addition of the alpha-antagonist phentolamine

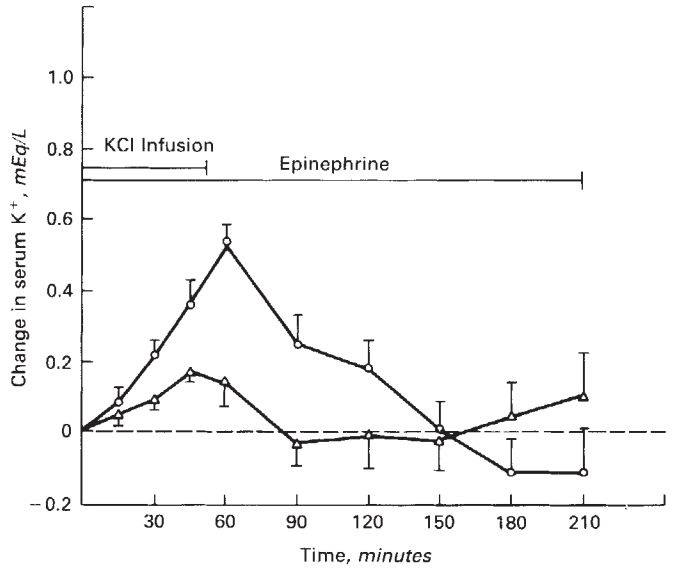


Fig. 4. *Effect of epinephrine on the increment in serum potassium induced by an intravenous potassium load.* Changes in serum potassium with potassium loading are denoted by open circles in the absence of epinephrine and by open triangles in the presence of epinephrine. Values plotted denote mean ± SEM in 5 subjects. The overall probability of the difference between treatments was <0.01 by repeated measure analysis. (Reproduced, by permission of the *New England Journal of Medicine* [302:431, 1980].)

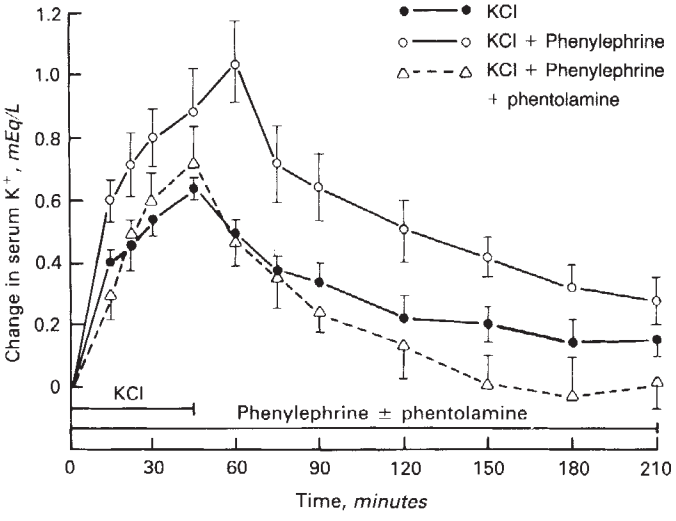


Fig. 5. *Effect of simultaneous phenylephrine and phentolamine on the increment in serum potassium (K^+) induced by an intravenous potassium chloride (KCl) load.* Subjects received phenylephrine in the dose that produced the highest elevation of the serum potassium level in a previous study. Values are mean levels (± SEM) in 7 subjects. The overall probability of the difference between phenylephrine and blockade with phentolamine was 0.005 by variance analysis. As compared with control studies, phentolamine blockade lowered potassium levels overall ($P < 0.05$ by variance analysis). (Reproduced by permission of the *New England Journal of Medicine* [311:145, 1984].)

blocked the rise in potassium produced by phenylephrine (Fig. 5) [66]. These findings are consistent with results from studies of phenylephrine administration in dogs [53] and with the early, brief hyperkalemic effect of epinephrine, which can be blocked by the alpha antagonist phenoxybenzamine [53, 55, 59]. These observations have been extended to exercise-induced hyperkalemia, in which beta blockade with propranolol augments and prolongs the potassium rise during muscular exercise [67–69], and in which alpha blockade with phentolamine diminishes the rise in potassium and lowers the potassium level during recovery [69]. Thus it seems likely that alpha-adrenergic stimulation impairs, and beta-adrenergic stimulation improves, the extrarenal disposal of acute potassium loads.

The cellular mechanism by which beta-adrenergic stimulation influences muscle cell uptake of potassium depends on specific binding to beta receptors and subsequent stimulation of adenylate cyclase. Adenylate cyclase in turn enhances cyclic AMP-mediated activation of sodium-potassium ATPase, resulting in sodium efflux and potassium influx [70–73]. The mediation of catecholamine action via cyclic AMP, in contrast to the action of insulin (which is independent of cyclic AMP), is consistent with the additive effects of insulin and epinephrine on potassium transport [30, 72].

Regulation of plasma potassium

Our current knowledge of the major factors controlling potassium homeostasis is summarized in Figure 6. When hyperkalemia occurs, as with increased potassium intake, reduced excretion, cell lysis, vigorous exercise, or movement of potassium out of cells, aldosterone is released. Aldosterone predominantly increases renal potassium excretion, but it also increases fecal potassium excretion and probably affects cellular potassium uptake as well. With large potassium loads, increased insulin secretion augments cellular potassium uptake. Even with smaller potassium loads, the basal insulin level is essential to facilitate cellular potassium uptake; thus one finds frequent impaired potassium tolerance and hyperkalemia in insulinopenic diabetic patients. Although the plasma epinephrine level does not rise with potassium loading [61], beta-adrenergic activity plays an important role in regulating cellular potassium uptake. Plasma catecholamine levels are relatively poor indicators of sympathetic nervous system activity, but norepinephrine turnover and urinary catecholamine excretion, which offer better estimates of adrenergic activity, are depressed by fasting and increased by feeding [74]. It seems likely that when potassium is ingested as part of a meal, the resulting increased beta-adrenergic activity together with insulin augment cellular potassium uptake and restore the plasma potassium level to normal. A similar beta-adrenergic effect appears to reverse the hyperkalemia of exercise by increasing cellular potassium uptake, thus counteracting the potassium release that occurs in contracting muscles [67–69]. Conversely, in hypokalemic states due to inadequate intake, to increased renal or extrarenal potassium losses, or to increased cellular uptake of potassium, aldosterone secretion is inhibited. This inhibition decreases renal and colonic potassium excretion, and possibly decreases cellular uptake of potassium as well (Fig. 6). Hypokalemia inhibits insulin secretion [75, 76] and further decreases cellular potassium uptake to help restore the plasma potassium level toward normal. Although no data document augmented alpha-adrenergic activity in hypokalemia, in potassium-depleted rats alpha receptors in skeletal muscle decrease sodium pump activity and thereby diminish muscle uptake of

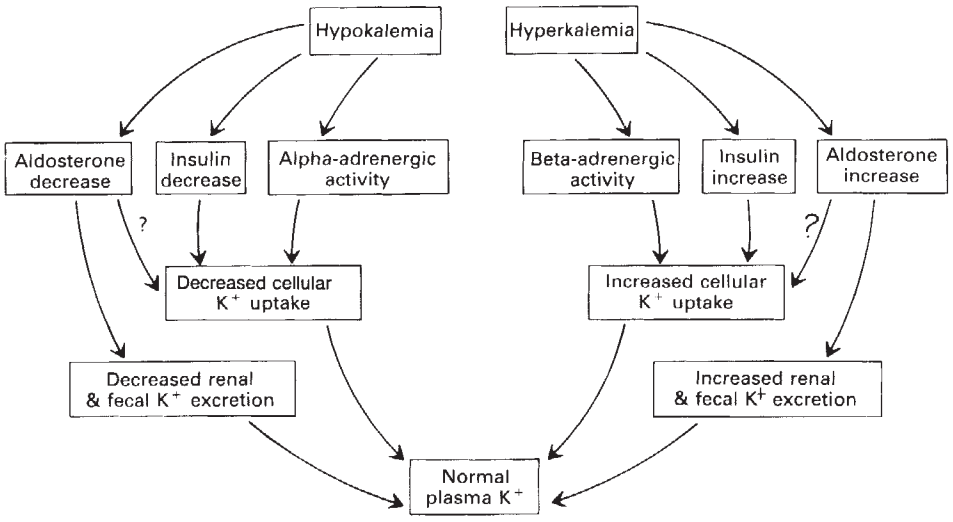


Fig. 6. *Schematic diagram of potassium homeostasis.* The major mechanisms that restore a depressed or elevated plasma potassium toward normal and their primary mode of action are depicted. The question marks denote uncertainty about the effect of aldosterone on cellular potassium uptake.

potassium [77, 78]. This effect is blocked by phentolamine and by other alpha-sympatholytic neural ablations [78]. It thus seems likely that alpha-adrenergic activity plays a role in potassium homeostasis by decreasing cellular potassium uptake, thus defending the plasma potassium level in chronic potassium depletion and also in the postexercise state, in which beta-adrenergic-mediated hypokalemia might occur [69].

Potassium homeostasis in the patient presented

In the patient presented today, why did the serum potassium increase so little with the first 300 mEq of potassium administered, and so much with the last 240 mEq? It is important to recognize that the relationship of the serum potassium to the total body potassium is not a linear one. The potassium deficits must be quite large, over 200 mEq, before substantial hypokalemia develops (Fig. 7) [79]. Therefore, the serum potassium level rises only slowly, despite administration of large quantities of potassium in severely depleted patients, until the total body potassium approaches normal. Thereafter the rise of the serum potassium with additional increments in total body potassium is much steeper (Fig. 7). It is reasonable to assume that the first 300 mEq of potassium this patient received (Fig. 1) resulted in the shallow rise of the serum potassium (shown at the left side of the curve in Figure 7), as expected in a severely depleted patient. Moreover, because this patient received most of the potassium load orally, we can't assume that her intestinal absorption was as rapid as normal, as severe potassium deficiency decreases gastrointestinal motility [80]. If gastric emptying was delayed because of the effect of hypokalemia on gastric smooth muscle, it is possible that only a portion of the potassium administered had been absorbed at the time that her serum potassium had risen to only 2.1 mEq/liter. The later influx of a larger proportion of the potassium load (when the relationship of serum potassium to total body potassium was on the steep portion of the curve in Figure 7) probably contributed to the marked rise in her serum potassium to 8.3 mEq/liter. Some of the mechanisms controlling potassium homeostasis

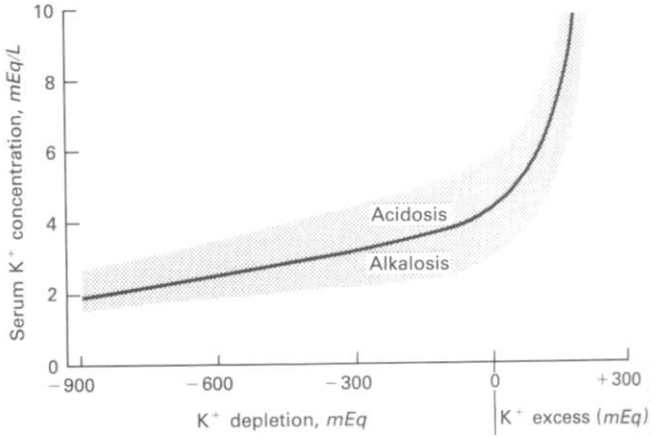


Fig. 7. *Approximate relationship between changes in total body potassium and the serum concentration of potassium in an adult.* The graph depicts a rough gauge of the degree of negative or positive potassium balance with hypokalemia or hyperkalemia in a 70 kg person. The shaded area shows that acidosis raises, and alkalosis lowers, the serum potassium concentration. (Reproduced, with permission, from Ref. 79.)

that I have described also could explain this phenomenon. The acute administration of 540 mEq of potassium to a 38 kg person could possibly cause a transient increase of serum potassium of as much as 14 mEq/liter, calculated on an apparent volume of distribution of about 1 liter/kg body weight [81], if the unwarranted assumption is made that all the potassium is absorbed rapidly from the intestine and none is excreted. Because such a large dose of potassium was administered to this small woman, it is apparent that avoidance of transient hyperkalemia depended on adaptive mechanisms that would increase potassium excretion, and more importantly, on the cellular uptake of potassium. Her potassium-depleted diet, initial hypokalemia, and urinary electrolytes showing adequate sodium and chloride levels but low potassium excretion all indicate that she was conserving potassium, and this clinical picture is consistent

Table 3. Extrarenal causes of hyperkalemia

Redistribution of potassium from intracellular to extracellular fluid
Acidosis
Insulin deficiency
Beta-adrenergic blockers (beta$_2$ or nonselective)
Alpha-adrenergic agonists
Vigorous exercise
Tissue necrosis
Chemotherapy cell lysis
Digitalis intoxication
Succinylcholine
Arginine infusion
Hyperkalemic periodic paralysis
Redistribution into the serum after phlebotomy (pseudohyperkalemia)
Hemolysis
Platelet release (thrombocytosis)
White blood cell release (leukemia)

Table 4. Extrarenal causes of hypokalemia

Gastrointestinal losses
Vomiting (mainly renal K^+ loss)
Diarrhea
Villous adenoma
Laxative abuse
Skin losses
Sweat
Burns
Redistribution of potassium from extracellular to intracellular fluid
Alkalosis
Insulin
Glucose infusion (endogenous insulin)
Beta-adrenergic agonists
Recovery from hypothermia or hypoxia
Recovery from exercise
Extensive physical conditioning
Barium poisoning
Familial hypokalemic periodic paralysis
Vitamin B_{12} therapy of pernicious anemia

with low aldosterone levels. Because the renal and extrarenal mechanisms take 3 to 4 days to maximally augment potassium excretion and cellular uptake when potassium intake is increased [3, 4], and because the aldosterone level was probably very low to begin with, a diminished ability to tolerate a potassium load is not unexpected in today's patient. Second, the potassium was administered without food to a woman whose basal and stimulated insulin levels were no doubt suppressed by anorexia nervosa and hypokalemia; her relative insulin deficiency also must have compromised cellular potassium uptake. Third, fasting or decreased food intake decreases sympathetic activity [74], and the decreased beta-adrenergic activity associated with the starved state would be expected to further impair cellular potassium uptake. Augmented alpha-adrenergic activity might have served as a protective mechanism to maintain the plasma potassium level while she was depleted, but it is possible that the stimulated alpha-adrenergic activity can persist long enough to impair potassium tolerance when potassium is administered so rapidly. In short, transient hyperkalemia from potassium replacement in patients with impaired potassium tolerance can be avoided if: (*1*) the quantity of potassium replaced is modified for patient size; (*2*) the doses of potassium given are sharply curtailed as the serum level rises; and (*3*) monitoring of the serum level is continued with equal diligence as normokalemia is approached.

Extrarenal causes of hyperkalemia

Although decreased urinary potassium excretion due to renal failure or mineralocorticoid insufficiency accounts for the majority of cases of hyperkalemia in clinical practice, extrarenal factors that can cause or contribute to hyperkalemia by redistribution are being recognized more frequently (Table 3). Because multiple mechanisms exist for promoting potassium tolerance, often the coexistence of several partial defects results in serious elevations of the plasma potassium. Diabetic patients are particularly prone to hyperkalemia because of the possible concomitance of insulin deficiency, acidosis, and autonomic insufficiency, together with mild renal failure or hyporeninemic hypoaldosteronism. In diabetic patients or others prone to hyperkalemia, each of these predisposing factors must be carefully assessed before one prescribes nonselective beta-adrenergic blockers or alpha-adrenergic agonists such as phenylephrine. The same considerations pertain to persons who engage in vigorous exercise; in this circumstance, exaggeration of the usually mild hyperkalemia of exercise can cause sudden death due to cardiac toxicity [1]. Tissue necrosis such as rhabdomyolysis, chemotherapy cell lysis [82], digitalis poisoning [83], succinylcholine [84] or arginine [85] administration, and the rare hyperkalemic periodic paralysis [86] all have been associated with hyperkalemia, which occurs when potassium shifts from the intracellular to the extracellular fluid compartment. The same phenomenon can occur in the test tube [87]; pseudohyperkalemia, easily diagnosed when caused by hemolysis, can be detected when caused by thrombocytosis or leukemia; one merely draws a blood sample into a heparin-treated tube to promptly measure a normal potassium level in the plasma, rather than the elevated serum level that occurs due to potassium release during clotting.

Extrarenal causes of hypokalemia

Extrarenal potassium losses via the gastrointestinal tract, or less commonly, the skin, are easily recognized causes of potassium wasting (Table 4), but redistribution of potassium from the extracellular fluid to the intracellular fluid is now known to be a more common cause of hypokalemia. Alkalosis causes renal potassium losses and a shift of potassium into cells; insulin, as well as glucose infusions (which stimulate endogenous insulin production), are frequent causes of hypokalemia. Beta-adrenergic agonists, such as epinephrine [53–57, 61], isoproterenol [53–55, 62], or terbutaline [62] can cause hypokalemia, and salbutamol can cause profound hypokalemia, which can be reversed by propranolol administration [88, 89]. Similarly, endogenous beta-adrenergic activity may decrease the plasma potassium in patients with acute myocardial infarction [65]; some researchers have proposed that this reduction in serum potassium increases the risk of rhythm disturbances in such patients. Recovery from hypothermia, hypoxia, or exercise can result in enough "overshoot" of cellular potassium uptake to cause transient hypokalemia [1]. Likewise, extensive physical training can produce mild hypokalemia as a form of potassium adaptation. This adaptation is manifested by enhanced muscle cell potassium uptake and by hyperpolariza-

tion without potassium deficiency [1]. The rare occurrence of barium poisoning with acid-soluble barium salts always causes hypokalemia because of the inhibition of cellular potassium efflux by barium, without suppression of potassium influx [90]. The severe hypokalemia produces muscle paralysis that is correctable by potassium administration, which restores the ratio of intracellular to extracellular potassium [90]. In familial hypokalemic periodic paralysis, muscle cell uptake of potassium is increased, causing hypokalemia during a paralytic attack [91], but treatment with potassium replacement is not often effective. Mild hypokalemia due to a rapid proliferation of bone marrow cells with cellular potassium uptake also has been described during vitamin B_{12} therapy of pernicious anemia [92].

In conclusion, an appreciation of the physiology of potassium homeostasis must include the factors that control extrarenal potassium distribution in addition to those affecting renal potassium excretion. Spontaneous or iatrogenic disorders of the mechanisms regulating potassium distribution often are unsuspected causes of hypokalemia and hyperkalemia; attention to these disorders helps ensure appropriate management of derangements of potassium metabolism.

Questions and answers

DR. VINCENT J. CANZANELLO (*Division of Nephrology, NEMCH*): Do you think that a direct action on the sodium-potassium ATPase pump is the mechanism of insulin- and/or catecholamine-stimulated potassium uptake by cells? Is there any evidence that these agents can alter membrane permeability to potassium independent of an effect on the pump?

DR. BROWN: Both the insulin effect and the beta catecholamine effect appear to be mediated by activation of the sodium pump. Insulin seems to have a direct stimulatory effect on sodium-potassium ATPase with rapid hyperpolarization of the cell [30]; this increased electronegativity is then sufficient to promote cellular uptake of potassium cations. The $beta_2$-adrenergic effect on the sodium pump is indirect, apparently mediated by stimulation of adenylate cyclase and generation of cyclic AMP, which activate sodium-potassium ATPase [70–73]. The effect of epinephrine on cellular potassium influx is enhanced by theophylline [70, 71] and blocked by ouabain [70]. Ouabain's ability to block sodium-potassium ATPase and simultaneously completely block epinephrine-induced potassium influx suggests that a sodium pump effect can account for this catecholamine action without changing membrane permeability to potassium. However, considerable evidence indicates that insulin alters cell membrane permeability, causing an increase in the relative permeability of potassium to sodium [93] and an increase in sodium-hydrogen exchange [31], which together favor cellular influx of potassium.

DR. RONALD PERRONE (*Division of Nephrology, NEMCH*): Dr. Brown, what do you advise your healthy patients who are taking beta blockers regarding exercise and hyperkalemia?

DR. BROWN: We know that beta blockers will augment and prolong the hyperkalemia of exercise. However, there are many healthy people taking beta blockers for hypertension who are exercising without adverse consequences yet identified. I have no advice for these patients unless they have a concomitant condition that impairs potassium tolerance. For patients prone to hyperkalemia, such as those with severe renal failure, hypoaldosteronism, or insulin-dependent diabetes mellitus, I would not favor using a beta blocker if the patient engages in the kind of vigorous exertion that could cause potentially serious potassium elevations, at least until we obtain more data under monitored conditions. I also would avoid causing combined defects in the potassium homeostatic mechanisms by the use of drug combinations that promote excessive hyperkalemia, such as angiotensin converting enzyme inhibitors, potassium-sparing diuretics, and beta blockers given together.

DR. KASSIRER: You mentioned one study of the influence of catecholamines on serum potassium. Have systematic studies of the effect of catecholamines at various levels of potassium deficiency been performed? Is there a titration curve of catecholamine effect, from the severely potassium-depleted animal on the one hand to a potassium-loaded animal on the other?

DR. BROWN: Not that I know of; such an experiment might examine the effects of alpha or beta blockers in animals with hypokalemia and hyperkalemia as a means of assessing the ambient tone of the alpha- or beta-adrenergic system. One might predict that with potassium depletion, alpha-adrenergic activity would be increased, thus maintaining the serum potassium level, and beta-adrenergic activity might be reduced. In this case, alpha blockade would decrease the serum potassium level, and beta blockade might be ineffective at increasing it. In potassium-loaded animals, the opposite would be expected; beta blockade would show a greater effect by blocking the heightened beta-adrenergic activity needed to prevent hyperkalemia. In our experiments in normal human subjects, neither alpha blockade with phentolamine nor beta blockade with propranolol had any acute effect on the serum potassium in the absence of a concomitant potassium load, although other groups have demonstrated a slight elevation of the serum potassium level due to redistribution out of cells in patients given propranolol chronically [60, 94].

DR. KASSIRER: I was trying to understand whether the influence of catecholamines, or perhaps epinephrine in particular, is different at different levels of potassium balance.

DR. BROWN: That is also untested to my knowledge. I presume that changes in receptor quantity or affinity, changes in sodium pump activity, or alterations in membrane permeability can have an influence on the effect of epinephrine in states of potassium depletion as compared with potassium excess. However, this question remains to be studied.

DR. KASSIRER: I acknowledge that stress-related epinephrine release can lower the serum potassium concentration in patients with acute myocardial infarctions, particularly in patients previously treated with diuretics, and I appreciate the concern that hypokalemia could increase the risk of life-threatening ventricular arrhythmias in these patients. But Drs. Harrington, Isner, and I were unable to find convincing evidence of a causal connection between diuretic use and serious arrhythmias following myocardial infarctions [95, 96]. Do you know of any such data?

DR. BROWN: Recently, Nordrehaug et al have reported several studies that address this crucial question. They found that following acute myocardial infarction, the serum potassium level correlated negatively with ventricular tachycardia and frequent unifocal premature ventricular contractions [97]. Furthermore, hypokalemia was more frequent when diuretics were used, and hypokalemia was associated with an increased frequency of ventricular fibrillation, although short-term mortality

following acute myocardial infarction was unchanged [98]. Because the serum potassium correlated negatively with the plasma epinephrine and rose more in the patients with myocardial infarctions who were treated with timolol [99], one could argue that beta blockade is protective in such patients, at least partly because of its effect on potassium.

DR. MADIAS: You mentioned that increments in plasma potassium of at least 1 mEq/liter are required to induce significant increases in plasma insulin. Has this issue been examined in the portal circulation, as opposed to merely in peripheral blood? Smaller changes in plasma potassium also might induce insulin secretion that is masked by the known large capacity of the liver for insulin extraction.

DR. BROWN: I know of no studies that examined portal vein insulin levels in animals given a small potassium load. This question is quite pertinent, because it has been shown that insulin initially stimulates the liver to take up potassium. Possibly this action would suffice for small potassium loads. The sustained insulin effect appears to be mediated by skeletal muscle, which may be the reservoir for larger potassium loads that increase peripheral insulin levels.

DR. NICOLAOS E. MADIAS: I should like to comment that recent data by Adrogué and colleagues have suggested a role for the endocrine pancreas to account for the disparity between organic acid acidosis and mineral acid acidosis regarding changes in plasma potassium concentration [100]. Whereas experimental ketoacidosis in the dog (characterized by normokalemia or hypokalemia) was associated with hyperinsulinemia, HCl-induced acidosis (characterized by hyperkalemia) was accompanied by elevated glucagon levels.

DR. BROWN: Thank you, Dr. Madias. That is an interesting observation.

DR. ANDREW S. LEVEY (*Division of Nephrology, NEMCH*): For our patients on dialysis, what are the relative influences of diet and alterations in extrarenal potassium metabolism on the serum potassium levels?

DR. BROWN: Extrarenal potassium tolerance is an important protective mechanism in patients on dialysis. To achieve a balance of total body potassium, the dialysis and gastrointestinal potassium excretion must equal dietary potassium intake in anuric patients. Most dialysis patients therefore require limitation of dietary intake, even though it is well recognized that colonic secretion of potassium can augment fecal potassium excretion [101]. Controversy exists, however, about the role of cellular potassium uptake in maintaining potassium tolerance between dialysis treatments in uremic patients. Studies with conflicting results showing impaired, normal, or increased extrarenal disposal of potassium loads were recently reviewed by DeFronzo and Bia [18]. It appears that resistance to catecholamine-stimulated potassium uptake and diminished sodium-potassium ATPase activity shown in red blood cells may impair potassium tolerance, whereas insulin-mediated potassium uptake is normal in uremic patients. The role of aldosterone in such patients remains to be clarified; data from our laboratory appear to document an acute, but not chronic, ability of aldosterone to improve disposal of a potassium load. Variation of extrarenal potassium tolerance from patient to patient might explain disparities in potassium levels that we often cannot ascribe to dietary indiscretion. More study is needed, but fortunately the cardiac resistance to hyperkalemic arrhythmias, which has been described in potassium-adapted animals, seems to protect some of our patients who manifest recurrent, severe hyperkalemia.

DR. MADIAS: You mentioned the importance of adrenergic activity in extrarenal potassium homeostasis. Are there any data suggesting that patients with autonomic insufficiency have disordered potassium tolerance?

DR. BROWN: Not that I know of.

DR. PERRONE: Some old data from Hayes, McLeod, and Robinson regarding colonic potassium excretion in chronic renal failure showed fairly substantial colonic potassium excretion in these patients [101]. The authors were unable to show consistent effects of spironolactone and thus could not draw any conclusions regarding the effect of aldosterone. Is there any additional information in this area?

DR. BROWN: Hayes et al documented elevated fecal potassium excretion in uremic patients, which accounted for a considerable proportion of the dietary intake [101]. The failure of spironolactone to affect fecal potassium excretion that this group described has been confirmed by data from our laboratory showing that spironolactone or deoxycorticosterone acetate failed to affect the high potassium-to-sodium concentrations in the feces of anephric dialysis patients. It seems likely that colonic adaptation augments potassium secretion in these patients and that this adaptation is independent of mineralocorticoid activity. This effect is similar to that in potassium-loaded rats that were adrenalectomized and that received only physiologic amounts of glucocorticoid [102]. However, total colonic potassium excretion depends on the wet weight of the feces, and because most of our dialysis patients were mildly constipated, possibly because of phosphate binders, the fecal potassium excretion was quite low, amounting to only about 10% of the potassium intake.

DR. PERRONE: Using a nephrectomized dog model, Sterns showed marked fluctuations in the plasma potassium associated with parallel changes in the serum insulin and catecholamines [58, 103]. Since the use of somatostatin blocked the changes in insulin but not the change in potassium, it seems that catecholamines must account for this effect. Are you aware of any data in humans showing similar large (1 to 2 mEq), minute-to-minute fluctuations in the plasma potassium level?

DR. BROWN: No, I'm not. In normal humans at rest we noted little variation in the serum potassium levels measured every 30 minutes; we have not looked for this phenomenon in our anephric patients in whom catecholamine levels would be high, as in most dialysis patients. Patients with acute, rather than chronic, renal failure might manifest variations in potassium levels analogous to those in nephrectomized dogs.

DR. MADIAS: Recent data have suggested that hyperkalemia-induced aldosterone secretion is dependent on angiotensin II [104]. Have studies examined the influence of captopril on potassium tolerance?

DR. BROWN: Captopril, and presumably other angiotensin converting enzyme inhibitors, can cause hyperkalemia by reducing aldosterone secretion in patients with renal insufficiency [105] or severe congestive heart failure [106]. As you have indicated, the mechanism appears to be a decrease of aldosterone secretion due to impaired sensitivity of the adrenal zona glomerulosa to potassium in vitro. This mechanism was demonstrated when angiotensin II was reduced in rats by pretreat-

ment with captopril [107]. No study has examined whether the elevation of the serum potassium with captopril is due to decreased renal excretion or to decreased extrarenal tolerance to potassium that has been caused by the hypoaldosteronism.

Reprint requests to Dr. R. Brown, Renal Division, Beth Israel Hospital, 330 Brookline Avenue, Boston, Massachusetts 02215, USA

References

1. KNOCHEL JP: Potassium gradients and neuromuscular excitability, in *The Kidney: Physiology and Pathophysiology*, edited by SELDIN DW, GIEBISCH G, New York, Raven Press, 1985, pp 1207–1221
2. EPSTEIN FH: Signs and symptoms of electrolyte disorders, in *Clinical Disorders of Fluid and Electrolyte Metabolism* (3rd ed), edited by MAXWELL MH, KLEEMAN CR, New York, McGraw-Hill, 1980, pp 499–530
3. SILVA P, BROWN RS, EPSTEIN FH: Adaptation to potassium. *Kidney Int* 11:466–475, 1977
4. ALEXANDER EA, LEVINSKY NG: An extrarenal mechanism of potassium adaptation. *J Clin Invest* 47:740–748, 1968
5. BURNELL JM, VILLAMIL MF, UYENO BT, SCRIBNER BH: The effect in humans of extracellular pH change on the relationship between serum potassium concentration and intracellular potassium. *J Clin Invest* 35:935–939, 1956
6. ADROGUÉ HJ, MADIAS NE: Changes in plasma potassium concentration during acute acid-base disturbances. *Am J Med* 71:456–467, 1981
7. PEREZ GO, OSTER JR, VAAMONDE CA: Serum potassium concentration in acidemic states. *Nephron* 27:233–243, 1981
8. LIEBMAN J, EDELMAN IS: Interrelationship of plasma potassium concentration, plasma sodium concentration, arterial pH and total exchangeable potassium. *J Clin Invest* 38:2176–2188, 1959
9. FRALEY DS, ADLER S: Isohydric regulation of plasma potassium by bicarbonate in the rat. *Kidney Int* 9:333–343, 1976
10. FRALEY DS, ADLER S: Correction of hyperkalemia by bicarbonate despite constant blood pH. *Kidney Int* 12:354–360, 1977
11. ROGERS TA, WACHENFIELD AE: Effect of physiologic acids on electrolytes in rat diaphragm. *Am J Physiol* 193:623–626, 1958
12. TOBIN RB: Varying role of extracellular electrolytes in metabolic acidosis and alkalosis. *Am J Physiol* 195:685–692, 1958
13. OSTER JR, PEREZ GO, VAAMONDE CA: Relationship between blood pH and potassium and phosphorus during acute metabolic acidosis. *Am J Physiol* 235:F345–F351, 1978
14. FULOP M: Serum potassium in lactic acidosis and ketoacidosis. *N Engl J Med* 300:1087–1089, 1979
15. ORRINGER CE, EUSTACE JC, WUNSCH CD, GARDNER LB: Natural history of lactic acidosis after grand-mal seizures. *N Engl J Med* 297:796–799, 1977
16. SCHWARTZ WB, ORNING KJ, PORTER R: The internal distribution of hydrogen ions with varying degrees of metabolic acidosis. *J Clin Invest* 36:373–382, 1957
17. SIMMONS DH, AVEDON M: Acid base alterations and plasma potassium concentration. *Am J Physiol* 197:319–326, 1959
18. DEFRONZO RA, BIA M: Extrarenal potassium homeostasis, in *The Kidney: Physiology and Pathophysiology*, edited by SELDIN DW, GIEBISCH G, New York, Raven Press, 1985, pp 1179–1206
19. HIATT N, YAMAKAWA T, DAVIDSON MB: Necessity for insulin in transfer of excess infused K to intracellular fluid. *Metabolism* 23:43–49, 1974
20. HIATT N, CHAPMAN LC, DAVIDSON MB, SKEINKOPF JA, MILLER A: Inhibition of transmembrane K transfer in ureter-ligated dogs infused with KCl. *Am J Physiol* 231:1660–1664, 1976
21. PETTIT G, VICK RL, SWANDER AM: Plasma K^+ and insulin: changes during KCl infusion in normal and nephrectomized dogs. *Am J Physiol* 228:107–109, 1975
22. SANTEUSANO F, FALOONA G, KNOCHEL JP, UNGAR RH: Evidence for a role of endogenous insulin and glucagon in the regulation of potassium homeostasis. *J Lab Clin Med* 81:809–817, 1973
23. DLUHY RG, AXELROD L, WILLIAMS GH: Serum immunoreactive insulin and growth hormone response to potassium infusion in normal man. *J Appl Physiol* 33:22–26, 1972
24. DEFRONZO RA, SHERWIN RS, DILLINGHAM M, HENDLER R, TAMBORLANE WV, FELIG P: Influence of basal insulin and glucagon secretion on potassium and sodium metabolism: Studies with somatostatin in normal dogs and in normal and diabetic human beings. *J Clin Invest* 61:472–479, 1978
25. DEFRONZO RA, FELIG P, FERRANNINI E, WAHREN J: Effect of graded doses of insulin on splanchnic and peripheral potassium metabolism in man. *Am J Physiol* 238:E421–E427, 1980
26. ZIERLER KL: Effect of insulin on potassium efflux from rat muscle in the presence and absence of glucose. *Am J Physiol* 198:1066–1070, 1968
27. GOLDFARB S, COX M, SINGER I, GOLDBERG M: Acute hyperkalemia induced by hyperglycemia: Hormonal mechanisms. *Ann Intern Med* 84:426–432, 1976
28. AMMON RA, MAY WS, NIGHTINGALE SD: Glucose-induced hyperkalemia with normal aldosterone levels. *Ann Intern Med* 89:349–351, 1978
29. SUNDERLIN FS, ANDERSON GH, STREETEN DHP, BLUMENTHAL SA: The renin-angiotensin-aldosterone system in diabetic patients with hyperkalemia. *Diabetes* 30:335–340, 1981
30. MOORE RD: Effects of insulin upon ion transport. *Biochem Biophys Acta* 737:1–49, 1983
31. MOORE RD: Stimulation of Na:H exchange by insulin. *Biophys J* 33:203–210, 1981
32. DAVIS JO, URQUHART J, HIGGINS JT JR: The effects of alterations of plasma sodium and potassium concentration on aldosterone secretion. *J Clin Invest* 42:597–609, 1963
33. BOYD JP, PALMORE WP, MULROW PJ: Role of potassium in the control of aldosterone secretion in the rat. *Endocrinology* 88:556–565, 1971
34. BIA M, TYLER K, DEFRONZO R: Regulation of extrarenal potassium homeostasis by adrenal hormones in rats. *Am J Physiol* 242:F641–F644, 1982
35. YOUNG DB, JACKSON TE: Effects of aldosterone on potassium distribution. *Am J Physiol* 243:R526–R530, 1982
36. DEFRONZO RA: Nephrology Forum: Hyperkalemia and hyporeninemic hypoaldosteronism. *Kidney Int* 17:118–134, 1980
37. LYMAN N, MULGAONKAR S, WALCER R, VISCUSO R, JACOBS MG: Effects of mineralocorticoids on extrarenal potassium homeostasis in anuric patients. *Kidney Int* 23:155, 1983
38. CHARRON RC, LEME CE, WILSON DR, ING TS, WRONG OM: The effect of adrenal steroids on stool composition, as revealed by *in vivo* dialysis of feces. *Clin Sci* 37:151–167, 1969
39. RICHARD P: Clinical investigation of the effects of adrenal corticosteroid excess on the colon. *Lancet* 1:437–441, 1969
40. THOMPSON BD, EDMONDS CJ: Comparison of effects of prolonged aldosterone administration on rat colon and renal electrolyte excretion. *J Endocrinol* 50:163–169, 1971
41. CHARNEY AN, KINSEY MD, MYERS L, GIANNELLA RA, GOTS RE: Na-K-activated adenosine triphosphatase and intestinal electrolyte transport. *J Clin Invest* 56:653–660, 1975
42. FUNDER JW, FELDMAN D, EDELMAN IS: Glucocorticoid receptors in rat kidney: the binding of tritiated-dexamethasone. *Endocrinology* 92:1005–1013, 1973
43. MARVER D: Assessment of mineralocorticoid activity in rabbit colon. *Am J Physiol* 246:F437–F446, 1984
44. KROZOWSKI ZS, FUNDER JW: Renal mineralocorticoid receptors and hippocampal corticosterone-binding species have identical intrinsic steroid specificity. *Proc Natl Acad Sci USA* 80:6056–6060, 1983
45. QUIRK SJ, GANNELL JE, FUNDER JW: Aldosterone-binding sites in pregnant and lactating rat mammary glands. *Endocrinology* 113:1812–1817, 1983
46. ARMANINI D, STRASSER T, WEBER PC: Characterization of aldosterone binding sites in circulating human mononuclear leukocytes. *Am J Physiol* 248:E388–390, 1985
47. FUNDER JW, FELDMAN D, EDELMAN IS: The roles of plasma binding and receptor specificity in the mineralocorticoid action of aldosterone. *Endocrinology* 92:994–1004, 1973
48. SIMPSON SAS, TAIT JF: Recent progress on methods of isolation, chemistry and physiology of aldosterone. *Recent Prog Horm Res*

11:183–219, 1955
49. Blair-West JR, Coghlan JP, Denton DA, Goding JR, Wright RD: The effect of aldosterone, cortisol and corticosterone upon the sodium and potassium content of sheep's parotid saliva. *J Clin Invest* 42:484–496, 1963
50. Emrich HM, Stall E, Rossi E: Aldosteronwirkung auf die Natriumchloridund Kalium Ausscheidung im Schweib von Pandreasfibrose-Patienten and Gesuden. *Klin Wochenschr* 48:966–973, 1970
51. Silva P, Spokes K: Sympathetic system in potassium homeostasis. *Am J Physiol* 241:F151–F155, 1981
52. Rosa RM, Silva P, Young JB, Landsberg L, Brown RS, Rowe JW, Epstein FH: Adrenergic modulation of extrarenal potassium disposal. *N Engl J Med* 302:431–434, 1980
53. Todd EP, Vick RL: Kalemotropic effect of epinephrine: Analysis with adrenergic agonists and antagonists. *Am J Physiol* 220:1963–1969, 1971
54. Pettit GW, Vick RL: An analysis of the contribution of the exocrine pancreas to the kalemotropic actions of catecholamines. *J Pharmacol Exp Ther* 190:234–242, 1974
55. Lockwood RH, Lum BKB: Effects of adrenergic agonists and antagonists on potassium metabolism. *J Pharmacol Exp Ther* 189:119–129, 1974
56. Lockwood RH, Lum BKB: Effects of adrenalectomy and adrenergic antagonists on potassium metabolism. *J Pharmacol Exp Ther* 203:103–111, 1977
57. Hiatt N, Chapman LW, Davidson MB: Influence of epinephrine and propranolol on membrane K transfer in anuric dogs with hyperkalemia. *J Pharmacol Exp Ther* 209:282–286, 1979
58. Sterns RH, Izzo JL, Mahany D, Turgeon K: Role of the adrenergic nervous system in hyperkalemia. *Kidney Int* 23:267, 1983
59. Lum BKB, Lockwood RH: Effects of nicotine and sympathomimetic amines on potassium intoxication. *J Pharmacol Exp Ther* 181:147–154, 1972
60. Pedersen G, Pedersen A, Pedersen EB: Effect of propranolol on total exchangeable body potassium and total exchangeable body sodium in essential hypertension. *Scand J Clin Lab Invest* 39:167–170, 1979
61. DeFronzo RA, Bia M, Birkhead G: The effect of epinephrine on potassium homeostasis. *Kidney Int* 20:83–91, 1981
62. Olsson AM, Persson S, Schroder R: Effects of terbutaline and isoproterenol on hyperkalemia in nephrectomized rabbits. *Scand J Urol Nephrol* 12:35–38, 1978
63. Struthers AD, Reid JL: The role of adrenal medullary catecholamines in potassium homeostasis. *Clin Sci* 66:377–382, 1984
64. Berand N, Marlin GE: Characterisation of adrenoreceptor subtype mediating the metabolic actions of salbutamol. *Br J Clin Pharmacol* 5:207–211, 1978
65. Brown MJ, Brown DC, Murphy MB: Hypokalemia from beta-2 receptor stimulation by circulating epinephrine. *N Engl J Med* 309:1414–1419, 1983
66. Williams ME, Rosa RM, Silva P, Brown RS, Epstein FH: Impairment of extrarenal potassium disposal by alpha-adrenergic stimulation. *N Engl J Med* 311:145–149, 1984
67. Carlsson E, Fellenius E, Lundborg P, Svensson L: Beta-adrenoreceptor blockers, plasma potassium, and exercise. *Lancet* 2:424–425, 1978
68. Lim M, Linton RAF, Wolfe CB, Band DM: Propranolol, exercise and arterial plasma potassium. *Lancet* 2:591, 1981
69. Williams ME, Gervino EV, Rosa RM, Landsberg L, Young JB, Silva P, Epstein FH: Catecholamine modulation of rapid potassium shifts during exercise. *N Engl J Med* 312:823–827, 1985
70. Clausen T, Flatman JA: The effect of catecholamines on Na-K transport and membrane potential in rat soleus muscle. *J Physiol* (Lond) 270:383–414, 1977
71. Clausen T: Adrenergic control of Na^+-K^+ homeostasis. *Acta Med Scand* (suppl) 672:111–115, 1983
72. Flatman JA, Clausen T: Combined effects of adrenaline and insulin on active electrogenic Na^+-K^+ transport in rat soleus muscle. *Nature* 281:580–581, 1979
73. Hokin LE: Reconstitution of "carriers" in artificial membranes. *J Membr Biol* 60:77–93, 1981
74. Landsberg L, Young JB: Fasting, feeding and regulation of the sympathetic nervous system. *N Engl J Med* 298:1295–1301, 1978
75. Rose JW, Tobin JD, Rosa RM, Andres R: Effect of experimental potassium deficiency on glucose and insulin metabolism. *Metabolism* 29:498–502, 1980
76. Helderman JH, Elahi D, Anderson DK, Raizes GS, Tobin JD, Shocken D: Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. *Diabetes* 32:106–111, 1983
77. Akaike N, Hirata A, Kiyohara T, Oyama Y: Neural regulation on the active sodium-potassium transport in hypokalaemic rat skeletal muscles. *J Physiol* (Lond) 341:245–255, 1983
78. Akaike N: Sodium pump in skeletal muscle: central nervous system-induced suppression by alpha-adrenoreceptors. *Science* 213:1252–1254, 1981
79. Valtin H: *Renal dysfunction: Mechanisms involved in fluid and solute imbalance*. Boston, Little, Brown, 1979, pp 89–111
80. Welt LG, Hollander W Jr, Blythe WB: The consequences of potassium depletion. *J Chronic Dis* 11:213–254, 1960
81. Sterns RH, Feig PU, Pring M, Guzzo J, Singer I: Disposition of intravenous potassium in anuric man: A kinetic analysis. *Kidney Int* 15:651–660, 1979
82. Muggia F: Hyperkalemia and chemotherapy. *Lancet* 1:602–603, 1973
83. Reza MJ, Kovick RB, Shine KI, Pearce ML: Massive intravenous digoxin overdosage. *N Engl J Med* 291:777–778, 1974
84. Gronert G, Theye R: Pathophysiology of hyperkalemia induced by succinylcholine. *Anesthesiology* 43:89–99, 1975
85. Bushinsky D, Gennari F: Life-threatening hyperkalemia induced by arginine. *Ann Intern Med* 89:632–634, 1978
86. Brooks JE: Hyperkalemic periodic paralysis. *Arch Neurol* 20:13–18, 1969
87. Wills MR, Fraser ID: Spurious hyperkalemia. *J Clin Pathol* 17:649–650, 1964
88. Obrien TAD, Fitzgerald-Fraser J, Lewin IG, Carroll RJM: Hypokalemia due to salbutamol overdosage. *Br Med J* 282:1515–1516, 1981
89. Connell JMC, Cook GM, McInnes GT: Metabolic consequences of salbutamol poisoning reversed by propranolol. *Br Med J* 285:779, 1982
90. Roza O, Berman LB: The pathophysiology of barium: Hypokalemic and cardiovascular effects. *J Pharmacol Exp Ther* 177:433–439, 1971
91. Zierler KL, Andres R: Movement of potassium into skeletal muscle during spontaneous attack in familial periodic paralysis. *J Clin Invest* 36:730–737, 1957
92. Lawson DH, Murray RM, Parker JLW: Early mortality in the megaloblastic anemias. *Q J Med* (new series) 41:1–14, 1972
93. Zierler KL, Rogus E, Hazelwood CF: Effect of insulin on potassium flux and water and electrolyte content of muscles from normal and hypophysectomized rats. *Gen Physiol* 49:433–456, 1966
94. Traub YM, Rabinov M, Rosenfeld JB, Treuherz S: Elevation of serum potassium during beta blockade: Absence of relationship to the renin-aldosterone system. *Clin Pharmacol Ther* 28:765–768, 1980
95. Harrington JT, Isner JM, Kassirer JP: Our national obsession with potassium. *Am J Med* 73:155, 1982
96. Kassirer JP, Harrington JT: Fending off the potassium pushers. *N Engl J Med* 312:785–787, 1985
97. Nordrehaug JE, Johannesen KA, von der Lippe G: Serum potassium concentration as a risk factor of ventricular arrhythmias early in acute myocardial infarction. *Circulation* 71:645–649, 1985
98. Nordrehaug JE, von der Lippe G: Hypokalemia and ventricular fibrillation in acute myocardial infarction. *Br Heart J* 50:525–529, 1983
99. Nordrehaug JE, Johannesen KA, von der Lippe G, Myking OL: Circulating catecholamine and potassium concentrations early in acute myocardial effect of intervention with timolol. *Am Heart J* 110:944–948, 1985
100. Adrogué HJ, Chap Z, Ishida T, Field JB: Role of the endocrine

pancreas in the kalemic response to acute metabolic acidosis in conscious dogs. *J Clin Invest* 75:798–808, 1985

101. HAYES CP JR, MCLEOD ME, ROBINSON RR: An extrarenal mechanism for the maintenance of potassium balance in severe chronic renal failure. *Trans Assoc Am Physicians* 80:207–216, 1967
102. BASTL CP, HAYSLETT JP: Augmented potassium secretion with potassium loading in aldosterone-deficient rats. *Proc 7th Int Congr Nephrol*, Montreal, 1978, p C7
103. STERNS RH: Oscillations of plasma K^+ and insulin during K^+ infusion in awake anephric dogs. *Am J Physiol* 243:F44–F52, 1982
104. PRATT JH: Role of angiotensin II in potassium-mediated stimulation of aldosterone secretion in the dog. *J Clin Invest* 70:667–672, 1982
105. TEXTOR SC, BRAVO EL, FOUAD FM, TARAZI RC: Hyperkalemia in azotemic patients during angiotensin-converting enzyme inhibition and aldosterone reduction with captopril. *Am J Med* 73:719–725, 1982
106. MASLOWSKI AH, IKRAM H, NICHOLLS MG, ESPINER EA: Haemodynamic, hormonal, and electrolyte responses to captopril in resistant heart failure. *Lancet* 1:71–74, 1981
107. PARKINSON CA, BELTON SJ, PRATT JH: The effect of captopril treatment on potassium-induced stimulation of aldosterone production in vitro. *Endocrinology* 114:1567–1570, 1984