EXTRARENAL K REGULATION:

PHYSIOLOGY, PATHOPHYSIOLOGY, AND CLINICAL RELEVANCE

by

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INTRODUCTION

Regulation of extracellular fluid potassium concentration is extremely important to the normal function of most cells in the body. This can best be seen by examining the Goldman equation which defines the cell membrane potential as a function of the ionic gradients across it.

$$\text{Potential Difference} = \frac{RT}{ZF} \ln \frac{P_{Na}[Na]_o + P_K[K]_o + P_{Cl}[Cl]_i}{P_{Na}[Na]_i + P_K[K]_i + P_{Cl}[Cl]_o}$$

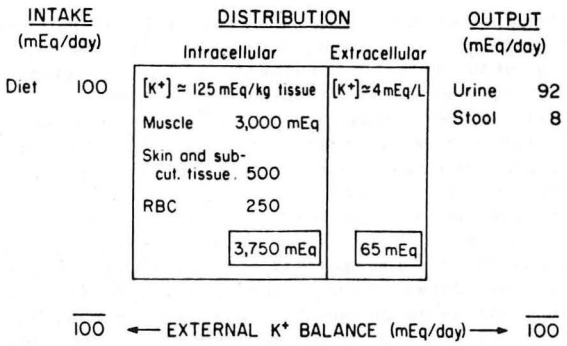
In most non-excitable cells, the potassium permeability is far greater than that of other ions, including sodium, chloride, calcium and bicarbonate. This is also true of excitable cells in the resting state. In this situation, the non-potassium terms in the Goldman equation become quantitatively small and drop out. This causes the cell membrane potential to approach the equilibrium potential for potassium, called the Nernst potential, shown below.

$$P.D. = RT/ZF \cdot \ln [K]_o/[K]_i$$

It can be seen from this equation that small changes in extracellular fluid potassium concentration will have a large effect on the potassium ratio and on the Nernst potential, thus affecting cell potential. Because of this, changes in extracellular potassium concentration will have large effects on the function of all cells, but especially that of cells whose function is exquisitely regulated by cell potential, such as nerve and muscle.

The kidney is the major organ for regulating total body potassium balance. Thus, changes in potassium intake lead to similar changes in renal potassium excretion so that total body potassium and extracellular potassium concentration are preserved. Because of this, almost all causes of chronic elevations or depressions in serum potassium can be related to disordered renal potassium handling. These conditions will not be discussed further at this time.

Figure 1 shows the distribution of potassium within the body. It can be seen here that an average potassium intake per person is approximately 100 mEq/day. This is balanced by an output of approximately 92 mEq/day in the urine and 8 mEq/day in the stool. Within the body, it can be seen that approximately 2% of total body potassium is present in the extracellular fluid. Thus, total extracellular fluid potassium is only approximately 65 mEq. This means that one heavy meal where a person ingests 65 mEq of potassium would be expected to lead to a doubling of extracellular fluid potassium concentration, which would certainly be fatal. While the kidney will eventually excrete this potassium, it is unlikely that it would do so rapidly enough to prevent life-threatening hyperkalemia. In addition, in patients with renal failure, ingestion of potassium would be expected to be uniformly fatal. In order to minimize these transient increases in plasma potassium concentration after K ingestion and prior to K excretion, the body has developed a number of physiologic mechanisms to shift potassium into cells pending its excretion.



Valtin, 1979

FIGURE 1

During this conference, I will discuss the physiologic mechanisms which regulate potassium movement into and out of cells and its relevance to potassium regulation and clinical medicine. As an introduction to this topic, I will present a series of electrolyte parameters recently obtained on a patient admitted to Parkland Hospital with diabetic ketoacidosis (Table 1).

TABLE 1

ELECTROLYTES FROM PATIENT ADMITTED TO PARKLAND HOSPITAL WITH DIABETIC KETOACIDOSIS

Time	[K]	pH	[HCO_3]	Anion Gap
2:00	8.0	6.93	7	29
3:00	6.0	6.96	8	27
4:00	4.5	7.10	12	25
5:00	4.5	----	12	24
7:00	4.3	7.08	11	23

On admission at 2 AM the patient had a serum potassium of 8.0 mEq/L with a blood pH of 6.93, serum bicarbonate of 7 mEq/L, a glucose of 1200 mg%, and an anion gap of 29 mEq/L with ketones present in serum and urine. As can be seen in the second column, during the first five hours of treatment, the serum potassium concentration dropped from 8.0 down to 4.3.

Potassium regulation in patients with diabetic ketoacidosis is extremely complex. All patients with marked hyperglycemia who have renal function will undergo an osmotic diuresis leading to total body potassium depletion. However, many patients with these conditions are not hypokalemic on presentation, and are sometimes hyperkalemic. While all agree that this is due to potassium shifts out of cells, there is much misunderstanding as to the mechanism of this potassium shift. When a patient such as this presents on the medical service and a medical student or house officer is asked why potassium has shifted out of cells, the most common answer is that if shifted in response to the ketoacidosis. The subsequent decrease in serum potassium concentration during treatment is then explained by correction of the acidotic state. Indeed, most of the textbooks used to teach medical students list this as the cause of potassium shifts. If one examines the electrolyte parameters of this patient, it is interesting to note that during the first hour the serum potassium concentration decreased by 2 mEq/liter in spite of no significant change in serum bicarbonate concentration or pH. This occurred in response to treatment with insulin and normal saline alone. During the second hour, the patient received intravenous bicarbonate in addition to insulin and saline, which raised the serum bicarbonate by 4 mEq/liter with a small increase in blood pH, and further corrected the serum potassium almost to normal. This patient, randomly provided to me by Dr. Fortin, Chief Medical Resident at Parkland Hospital, demonstrates something which has been observed many times, a dissociation between the K shift back into cells and a correction of the metabolic acidosis (1).

pH-DEPENDENT POTASSIUM SHIFTS: METABOLIC ACIDOSIS

The thesis which has generally been taught in medical schools is that acidosis causes potassium to shift out of cells and alkalosis causes potassium to shift into cells. This would theoretically occur by some mechanism equivalent to potassium-hydrogen exchange. Thus, an acid load added to the extracellular fluid would cause hydrogen ions to enter the cell, in effect buffering the extracellular acidosis. In exchange for the hydrogen entering the cell, potassium would come out. Induction of extracellular alkalosis would cause hydrogen to move from cells into the extracellular fluid thus buffering the extracellular fluid alkalosis. This would then lead to K uptake into the cells.

The basis for this theory can be attributed to the classic experiments of Swan and Pitts (2). The results of their studies are summarized in Figure 2.

HCl INFUSION INTO NEPHRECTOMIZED DOGS

Weight = 18.9 kg

Infusion = 180 mmoles HCl

pH_{final} = 7.07

$\Delta[K]_{plasma}$ = +5 mEq/L

ΔTotal extracellular K = +28 mEq

Swan and Pitts, 1955

FIGURE 2

Nephrectomized dogs having an average weight of 18.9 kg received an infusion of 180 mmoles of HCl. This caused blood pH to decrease to 7.07 and was accompanied by an increase in plasma potassium concentration of 5 mEq/liter. These investigators measured extracellular fluid volume using total chloride space and total sulfate space, and found that HCl infusion caused a shift of 28 mEq of K from the intracellular fluid into the extracellular fluid. These results could not be attributed to the kidney as the animals were nephrectomized just prior to the infusion.

Similar studies were performed by Tobin (3) in the nephrectomized cat. Tobin found that infusion of 2.5 to 9.6 mEq acid/kg body weight caused the blood pH to decrease from 7.41 to 6.89. In these studies, plasma potassium concentration increased by 1.2 mEq/liter. Measurements of extracellular fluid volume showed an increase of total extracellular K of 0.3 mEq/kg body weight. In addition, Tobin measured muscle potassium concentration and showed that the HCl infusion caused a decrease in muscle potassium concentration of 2.3 mEq/kg.

In order to further examine the mechanism of this shift, Rogers (4) examined the effect of extracellular fluid pH on muscle cell composition in vitro. Rat hemidiaphragms were incubated in solutions of varying pH and their potassium content compared with their respective hemidiaphragm incubated in fluid of pH 7.4. Extracellular fluid pH was varied by addition of HCl or sodium bicarbonate in these studies. As can be seen in Figure 3, decreasing extracellular fluid from pH 7.4 to pH 6.4 leads to a progressive loss of potassium from the muscle cells. Increasing extracellular fluid pH to 7.6 leads to an accumulation of potassium in the cells. The drop in intracellular potassium concentration at very high extracellular pHs was attributed to a toxic effect on the cells, possibly related to changes in extracellular fluid ionized calcium concentration (bicarbonate complexes with calcium).

In summary, these studies demonstrated that addition of mineral acid to the extracellular fluid caused a shift of potassium from the intracellular fluid to the extracellular fluid. While these studies only used mineral

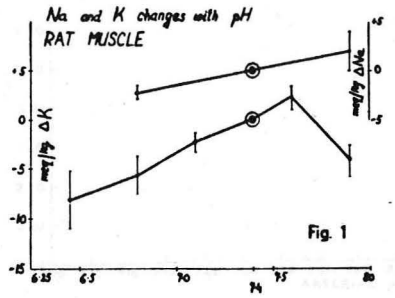


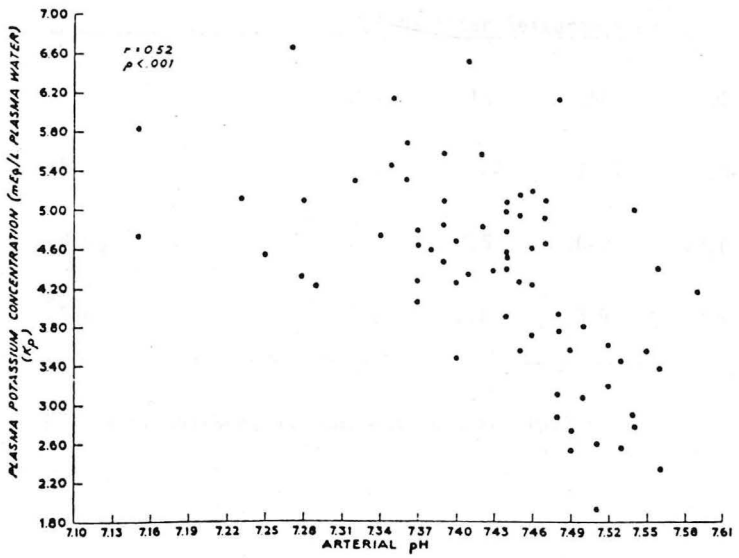
FIGURE 3

Rogers, 1957

acids, they were interpreted to be relevant to acidosis in general. This leap of faith rested largely on the observation that patients with diabetic ketoacidosis and lactic acidosis tended to shift potassium out of their cells. To test the relevance of these observations in humans, Burnell and co-workers (5) infused solutions of varying pH into humans, and found that lowering blood pH was associated with increased serum potassium concentration and raising blood pH was associated with decreased serum potassium concentration. Based on these results, it has been suggested that in order to interpret the serum potassium concentration, it is necessary to correct it for the blood pH. They suggested that approximately 0.7 mEq/liter should be added to the observed serum potassium for every 0.1 pH unit increase above 7.4.

To further examine the role of blood pH in the modulation of serum potassium, Leibman and Edelman (6) examined a large number of patients whose serum pH and potassium concentration covered a broad range. Without performing any maneuvers on these patients, they found a fairly good correlation between serum potassium concentration and blood pH (Figure 4). As these patients were not preselected for their type of acidosis, these studies seem to confirm the role of extracellular fluid pH as a regulator of serum potassium, presumably through regulation of shifts in and out of cells.

The first suggestion that organic acidoses may be different than mineral or inorganic acidoses came from a study, originally published in 1949, but



Leibman and Edelman, 1959

FIGURE 4

largely ignored. In this study, Ward and Call (7) implanted electrodes into rat brains and followed blood composition during and following a seizure. These investigators found that despite severe lactic acidosis, there was no significant change in plasma potassium concentration. More recently, in 1977 Orringer and co-workers (8) reported similar results in humans. These studies, the results of which are shown in Table 2, found that in humans followed after a seizure, a severe metabolic and respiratory acidosis developed which resolved over 60 minutes. During this time, however, there were no changes in serum potassium concentration. These studies taken together suggest that lactic acidosis secondary to seizures is not associated with shifts of potassium out of cells. This would imply that the mere presence of lactic acidosis does not require a K shift out of cells.

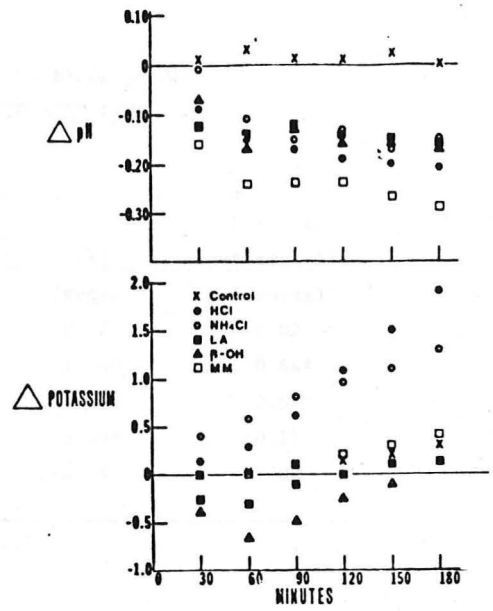
TABLE 2

PLASMA ELECTROLYTES IN POSTICTAL HUMANS

	Time after Seizure (min)			
	0-4	15	30	60
pH	7.14	7.24	7.31	7.38
$[HCO_3]_p$	17.1	17.5	20.0	23.6
$[K]_p$	3.8	3.8	3.9	3.9

Orringer, Eustace, Wunsch, and Gardner, 1977.

To examine this more directly, Oster, Perez, and Vaamonde (9) examined the effect of different acid infusions on serum pH and potassium concentration in dogs. These results shown in Figure 5, demonstrated that infusions of HCl, NH_4Cl, lactic acid, beta hydroxybutyric acid, and methylmalonic acid all produced similar decreases in blood pH. However, only HCl and NH_4Cl caused an increase in serum potassium concentration. Beta hydroxybutyric, methylmalonic acid, and lactic acid infusions did not cause the increase in plasma potassium concentration. Although these animals had normal renal function, urine studies showed no differences in renal potassium excretion with the acid infusions. Thus, these studies suggested that mineral acid infusions lead to shifts of potassium out of cells whereas organic acid infusions do not. In subsequent studies, Oster and co-workers (10) found that if these infusions were extended over 6 hours, results were similar.



Oster, Perez, and Vaamonde, 1978

FIGURE 5

In order to follow up on these observations it is necessary to measure extracellular fluid volume. For instance, it is possible that organic acidoses lead to potassium shifts but that simultaneous shifts of sodium and water out of cells dilute the potassium and thus prevent a rise in serum potassium concentration. This thesis has been tested in a more complete set of studies performed by Tobin (11). As is typically the case in clinical medicine, these more complete studies were performed 20 years before Oster's observations but remained ignored by clinical medicine. Tobin infused similar amounts of HCl, NH_4Cl, acetic acid, and lactic acid into nephrectomized cats (Table 3). Similar to the results of Oster and co-workers, Tobin found that all four acids caused similar decreases in blood pH, but only HCl and NH_4Cl caused a significant increase in serum potassium concentration. When extracellular fluid volume was measured, it was determined that HCl and NH_4Cl caused a shift of K out of cells into the extracellular fluid, whereas acetic acid and lactic acid caused no K shifts (Table 3).

Rogers and Wachenfeld (12) examined this question using rat diaphragms in vitro. These results are shown in Table 4. As discussed above, when extracellular fluid pH was lowered by addition of HCl there was a loss of potassium from the muscle. However, when extracellular fluid pH was lowered

TABLE 3

EFFECT OF ACID INFUSION ON BLOOD pH AND SERUM [K] IN NEPHRECTOMIZED CATS

Acid Infused	ΔpH	Δ[K] (meq/L)	K shift out of cells (meq/kg)
Control	-0.02	0.12	0.02
HCl	-0.51*	1.24*	0.44*
NH_4Cl	-0.33*	2.23*	0.58*
Acetic	-0.25*	-0.65*	-0.11
Lactic	-0.35*	-0.04	0.02

Tobin, 1958

TABLE 4

EFFECT OF ACID pH ON MUSCLE K CONTENT IN VITRO (RAT DIAPHRAGM)

Acid Added to Extracellular Fluid	Δ K Content (mEq/kg wet tissue)
HCl	-5.6
Acetic acid	-0.1
B-OH butyric acid	-0.5
Lactic acid	+0.6

Rogers, Wachenfeld, 1958

by addition of acetic acid, beta-hydroxybutyric acid or lactic acid, no shift of potassium out of cells was observed. These results, along with those of Tobin (11) and Oster and colleagues (9,10), demonstrate that whereas inorganic acid infusion leads to a shift of potassium out of cells, organic acid infusion does not.

The best explanation for these observations is shown in Figure 6. When HCl is added to the extracellular fluid, there is a marked decrease in extracellular fluid pH which initially is not accompanied by any change in cell pH. Cell membrane transporters respond to this by moving hydrogen into the cell. Because chloride is unable to enter most cells, electroneutrality is achieved in some manner (see below) by cation efflux from the cell. As discussed throughout this manuscript, a portion of the electroneutrality is achieved by K efflux from cells. Although not discussed in this manuscript, a major portion of electroneutrality is achieved by sodium efflux from the cells (2,3). Because of the large pool of extracellular sodium, this sodium efflux is more subtle clinically than the potassium efflux.

Organic acid infusions have a different effect on the cell. Because organic acids are lipid soluble in their protonated form, they are able to enter the cell intact and cause a similar acidification of intracellular and extracellular fluid. There is thus no gradient across the plasma membrane hydrogen transporters, no H^+ uptake, and no need for cation efflux. This

NONIONIC VERSUS IONIC DIFFUSION

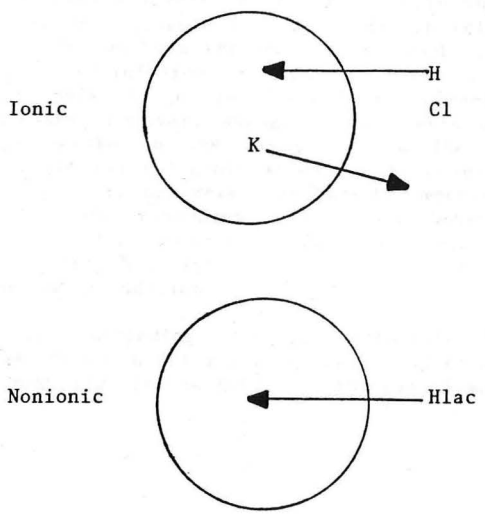


FIGURE 6

thesis rests on the ability of organic acids to diffuse across plasma membranes in their acid forms. Because most organic acids have pKs of 3.5 to 4.5, concentrations of protonated acids will be 3-4 orders of magnitude less than the dissociated form of the acid. However, Gutknecht and co-workers (13,14) have demonstrated in extensive studies that although protonated organic acid concentrations are extremely low, permeability across lipid bilayers is extremely high, such that diffusive fluxes can be large.

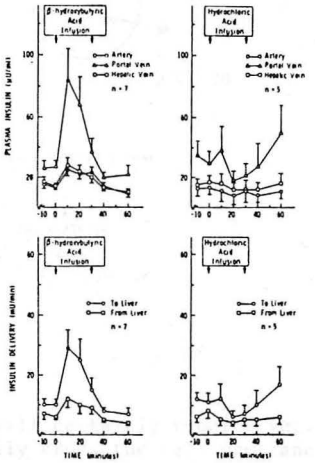
As organic acid infusions do not lead to K shift out of cells it is unlikely that hyperkalemia seen in organic acidoses is due to the acidosis. In addition, one other problem exists with respect to the theory that there were K shifts in organic acidoses. The thesis, as stated above, was that organic acidoses caused an increase in hydrogen ion concentration outside the cells which was buffered by H moving intracellularly, secondarily causing K to move out of cells. However, organic acids are not formed in the extracellular fluid. They are actually formed intracellularly and if any H movements occur they are in the net cell efflux direction. Thus, if organic acidoses could lead to K shifts, one would expect the more likely direction of the K shift would be into the cells. Similarly, during correction of ketoacidosis and lactic acidosis, cells are taking up these acids for metabolism, and the expected K shift would be out of the cells, opposite to the observed direction.

One other factor may contribute to the difference between organic and inorganic acidoses. As will be discussed below, insulin is an important regulator of potassium shifts in and out of cells. In their original infusion studies, Oster and colleagues (10) found no difference in the response of insulin levels to HCl and lactic acid infusions. In more recent studies, Adrogue et al (15) compared HCl infusions to infusions of beta-hydroxybutyric acid. As in previously described studies, HCl infusion caused an increase in serum K concentration whereas beta-hydroxybutyric acid infusion did not. When these authors measured insulin levels in hepatic artery, portal vein and hepatic vein, they found that beta-hydroxybutyric acid infusion led to increased insulin levels in the portal vein which were no longer detected by the hepatic vein (Figure 7). This insulin release was not observed with HCl infusion. The authors therefore postulated that insulin release in response to organic acid infusion could enhance potassium uptake in the liver, yet lead to undetectable changes in plasma insulin levels in the peripheral blood. In these studies, however, Adrogue et al. were unable to demonstrate enhanced potassium uptake in the liver. Since the differential response between organic acids and inorganic acids can be observed in rat diaphragm muscle in vitro (12), it is unlikely that hormonal mechanisms are key in the difference between the two responses. They may, however, contribute. It is also possible that the response of insulin levels to beta-hydroxybutyric acid is specific to beta-hydroxybutyric acid, rather than being a generalized response to organic acid addition.

Before proceeding, it is worthwhile to discuss briefly possible mechanisms by which HCl infusion could lead to a shift of potassium out of the cell. Initially, it was felt that the plasma membranes of muscle cells

possessed a K-H exchanger (Figure 8a). Concern over such a thesis was raised by Adler and Fraley (16) who pointed out that the relationship between hydrogen and potassium movement was extremely complex and not likely to be attributable to a simple coupling. In addition, no such simple K-H exchanger has been identified in muscle. It is interesting to note that an ATP-coupled K-H exchanger has been found to be the apical membrane mechanism for gastric hydrogen ion secretion.

A second possible mechanism of coupling between H and K is that of parallel H and K conductances (Figure 8b). According to this theory, acidification of the



Adrogue, Chap, Ishida, and Field, 1985

FIGURE 7

extracellular fluid would cause hydrogen ions to diffuse into the cell. This would lead to cell depolarization which would drive either a cation out of the cell or an anion into the cell. Because the major conductance on the plasma cell membrane is to potassium, the most likely ion to move would be potassium. The major problem with this theory is that it postulates a significant hydrogen ion conductance or leak on the plasma membrane. Such a large hydrogen ion permeability has never been found and would seem unlikely as it would make it extremely difficult to maintain a normal cell pH of 7.0. This mechanism, therefore, seems unlikely. It should also be noted that both of the first two mechanisms would not be expected to lead to a shift in sodium as well as potassium into the extracellular fluid. As discussed above, Swan and Pitts (2) and Tobin (3) both found that sodium shifts were actually of greater magnitude than potassium shifts.

The third mechanism (Figure 8c) would be the one that I would favor at this time. It relies on two transporters which have both been shown to be present in the plasma membrane of most cells including muscle. Na/H antiport has been found to be an almost universal transport mechanism for defense of cell pH in mammalian cells (17). I would postulate that under basal conditions the Na/H antiporter runs at a finite rate, allowing sodium entry and driving hydrogen ions out at a slow rate. Sodium which enters on this transporter would then be removed from the cell by the NaK ATPase. Acidification of the extracellular medium will lead to a slowing of the Na/H antiporter causing pH to slowly decrease in the cell and sodium concentration to go down in the cell. This would explain the shift of sodium seen in HCl acidosis. Then, in response to a decreased sodium concentration in the cell, the NaK ATPase would slow down. This will lead to decreased uptake of potassium and thus a net shift of K from the intracellular to the extracellular compartment. This thesis is appealing in that it utilizes

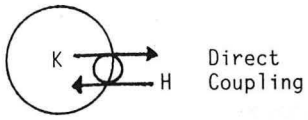


FIGURE 8a

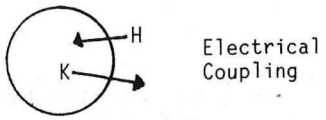


FIGURE 8b

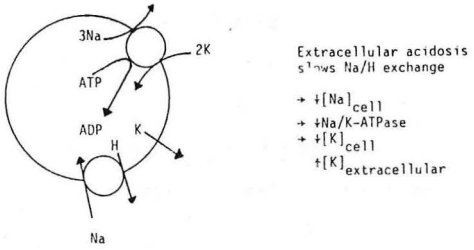


FIGURE 8c

transport mechanisms known to exist, but will certainly require verification. Once again, because organic acids can freely cross the cell membrane, organic acid addition will not alter the pH gradient across the cell and thus will not alter the rate of the Na/H antiporter leading to the above described secondary effects.

In summary, inorganic acidoses are associated with a potassium shift out of cells. While the mechanism of this effect is not clear, I feel that the best explanation is a pH gradient-dependent alteration in the rate of the Na/H antiporter with secondary effects on NaK ATPase. Organic acidosis is not associated with K shifts out of cells. The major reason for this is that organic acids are able to freely permeate plasma membranes and thus do not alter pH gradients across these membranes. In addition, organic acids are formed in the cell and thus do not require net cell entry. Lastly, changes in insulin secretion in response to organic acid infusion may also contribute somewhat to preventing K shifts.

pH-DEPENDENT K SHIFTS: SODIUM BICARBONATE INFUSION

Classical teaching in textbooks is that $NaHCO_3$ should be administered to patients with life-threatening hyperkalemia because it leads to shifts of potassium into cells. When one reviews the literature it becomes apparent that this is only half true. Figure 9 shows the results of experiments by Swan, Axelrod, Seip, and Pitts (18), where $NaHCO_3$ was infused into nephrectomized dogs. Dogs weighing an average of 21.6 kg received an infusion of 400 mmoles of $NaHCO_3$, resulting in a final blood pH of 7.65. This was associated with a decrease in the plasma potassium concentration of 0.5 mEq/liter, consistent with its therapeutic value in hyperkalemia. However, the mechanism of this effect is not as taught. In fact, Swan and colleagues (18) found no significant shift in potassium into cells but rather found an increase in extracellular fluid volume which diluted the extracellular fluid potassium and lowered the potassium concentration.

FIGURE 9

$NaHCO_3$ INFUSION INTO NEPHRECTOMIZED DOGS

Weight = 21.6 kg

Infusion = 400 mmoles

pH_{final} = 7.65

$\Delta[K]_{plasma}$ = -0.5 meq/L

Δ Total extracellular K = +4 meq

Swan, Axelrod, Seip, and Pitts, 1955

Tobin (11) performed similar studies in nephrectomized cats and found similar results (Table 5). Infusion of NaOH or $NaHCO_3$ led to an increase in blood pH, associated with a decrease in plasma potassium concentration. Once again, there was no shift of potassium into or out of cells but rather merely an increase in extracellular fluid volume diluting extracellular potassium. NaCl infusion which caused a similar increase in extracellular fluid volume, did not lower the serum potassium because it caused a shift of potassium out of cells. It thus appears that the response of serum potassium concentration to sodium bicarbonate infusion is complex and multifactorial. $NaHCO_3$ infusion

TABLE 5

EFFECT OF ISOHYDRIC AND ALKALINE INFUSIONS ON BLOOD pH AND SERUM [K] IN NEPHRECTOMIZED CATS

Infusate	Δ pH	Δ [K] (meq/L)	K shift out of cells (meq/kg)
NaOH	0.17*	-0.39	-0.05
$NaHCO_3$	0.22*	-0.37	0.03
NaCl	-0.05	+0.81*	0.45

Tobin, 1958

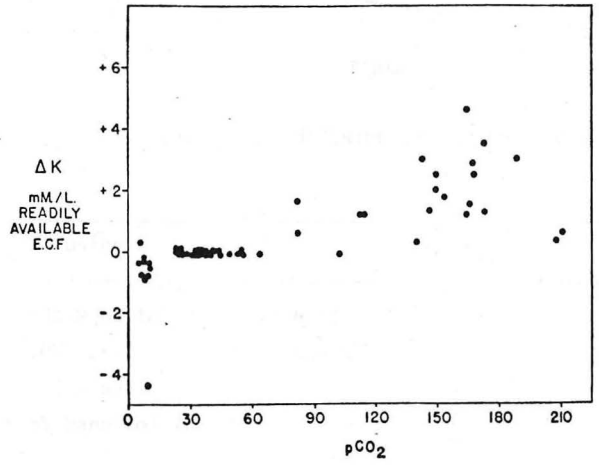
is an effective method of treating life-threatening hyperkalemia. It appears, however, that this is not due to a shift of potassium into cells but rather merely to expansion of extracellular fluid volume leading to dilution of the extracellular fluid potassium concentration. NaCl injection, which would be expected to cause the same dilution, is not useful therapeutically because it leads to a K shift out of cells. The mechanism of the K shift in response to NaCl infusion is not clear.

pH-DEPENDENT K SHIFTS: RESPIRATORY ACIDOSIS

Based on the above discussion, changes in blood CO_2 concentration would be expected to not cause potassium shifts. CO_2 is an extremely permeant acid, should permeate all cells easily and not lead to any significant pH gradients across cell plasma membranes. This, however, is not what has been observed. As shown in Figure 10, when pCO_2 was varied in nephrectomized dogs, Giebisch, Berger and Pitts (19) found that increases in pCO_2 led to an increase in serum potassium concentration which was due to potassium shift out of cells.

While these results conflict with that predicted from our proposed thesis, it may be that respiratory acidosis is more complex than simple organic acidosis. Indeed, this conclusion is suggested by the results of Rogers and Wachenfeld (12). These authors examined the effect of extracellular pH on muscle potassium in rat diaphragms incubated in vitro. As

FIGURE 10



Giebisch, Berger, and Pitts, 1955

discussed previously, they found that acidification of the extracellular medium with HCl caused potassium loss from the muscle. However, these investigators found that acidification of the extracellular medium by raising CO_2 from 2% to 10% caused no shift in potassium, consistent with its ability to permeate cells. These studies suggest that respiratory acidosis does not directly lead to K shifts. However, due to other mechanisms present in the body, possibly catecholamine release (see below) the net result is shift of K out of cells.

ROLE OF HYPERTONICITY

Based on the above discussion, it should now be painfully clear that in our patient with diabetic ketoacidosis, the ketoacidosis was not the cause of the potassium shift out of cells, and treatment for correction of the ketoacidosis was not responsible for the K shift back into cells. Since there is no question but that K shifts do occur in diabetic ketoacidosis, we must now discuss the mechanism of these shifts. Two probable causes of these shifts are insulin deficiency and hyperglycemia. We will begin here with a discussion of the role of hypertonicity in K regulation.

Moreno, Murphy, and Goldsmith (20) examined the effect of hypertonic infusions on serum potassium in human subjects. Some of their results are shown in Table 6. Infusion of 10% mannitol in 75 mmoles NaCl caused a small drop in the plasma bicarbonate concentration and a rise in the plasma potassium concentration. To rule out an effect of the dilutional acidosis, a

TABLE 6

EFFECTS OF HYPERTONIC INFUSIONS ON K

Infusion	$\Delta[HCO_3]_p$	$\Delta[K]_p$
10% Mannitol in 75 mM NaCl	-2.8*	+0.6*
10% Mannitol in 75 mM $NaHCO_3$	+1.8	+0.3*
2.25% NaCl	+0.8	+0.4*
5% Mannitol	-1.5	+0.4*

Moreno, Murphy, and Goldsmith, 1964

second experiment was done with 10% mannitol and 75 mmoles $NaHCO_3$. This did not affect the plasma bicarbonate concentration but still caused a rise in plasma potassium concentration. Both of these infusions caused plasma osmolality to rise by approximately 10 mOsm/liter and serum sodium concentration to decrease by approximately 10 mOsm/liter. A hypertonic saline infusion, shown in the third row, did not cause a change in the plasma bicarbonate concentration, yet caused a significant increase in serum potassium concentration. In these studies, once again, osmolality rose by approximately 10 mOsm/liter, and in addition, serum sodium rose by 6 mEq/liter. Thus, it appears from these studies that any hypertonic solution will cause an increase in plasma potassium concentration.

They also examined the effect of isotonic infusions on serum potassium concentration. In the fourth row of Table 6 are shown the results of 5% mannitol infusion. This caused no change in plasma bicarbonate concentration but an increase in plasma potassium concentration. This was associated with no change in plasma osmolality and a decrease in plasma sodium concentration of 8 mEq/liter. The decrease in plasma sodium concentration suggests water movement out of cells. Isotonic saline, on the other hand, caused no change in plasma potassium concentration and isotonic $NaHCO_3$, as discussed previously, caused a small decrease in plasma potassium concentration.

While the above studies suggest a shift of potassium out of cells when hypertonic solutions or impermeant solutes are infused into the extracellular fluid, these studies did not measure extracellular fluid volume. Subsequent studies by Mackoff and co-workers (21) examined this question by infusing either hypertonic saline or hypertonic mannitol solutions into nephrectomized dogs. Total body water, extracellular fluid volume, and intracellular pH were measured by the distribution of ^{3}H water, ^{36}Cl, and ^{14}C DMO respectively. The results are shown in Table 7. Hypertonic infusions of NaCl or mannitol caused an increase in the concentration of potassium in the extracellular fluid in spite of markedly different effects on sodium concentration. This was associated with an increase in extracellular fluid volume and a decrease in intracellular fluid volume, such that there was a calculated shift of potassium into the extracellular fluid of 0.8 mEq/kg body weight.

In addition, this maneuver was associated with changes in the hydrogen ion gradient between the intracellular and extracellular fluid, with extracellular acidosis and intracellular alkalosis. The changes in the hydrogen ion gradient could all be explained by dilution of extracellular bicarbonate (extracellular dilutional acidosis) and concentration of intracellular bicarbonate (intracellular contraction alkalosis).

Based on this data, two possible mechanisms for the observed K shifts with states of hypertonicity arise. The first is shown in Figure 11a. Increases in extracellular fluid tonicity lead to a shrinkage of the cell, which concentrates intracellular potassium concentration. The rise in intracellular potassium concentration can then provide a driving force for potassium efflux. To comprehend the possible magnitude of such an effect, one needs to realize that a shift of 2% of intracellular potassium into the extracellular fluid will double the extracellular fluid potassium concentration.

TABLE 7

EFFECTS OF HYPERTONIC INFUSIONS
IN NEPHRECTOMIZED DOGS

	750 mM NaCl	1.5 M Mannitol
$\Delta[Na^+]_e$, mEq/L	+21.2*	-34.3*
$\Delta[K^+]_e$, mEq/L	+1.8*	+1.6*
ΔTotal ECF K, mEq/kg BW	+0.80*	+0.82*
ΔECF_{vol}, %BW	+6.8*	+8.3*
ΔICF_{vol}, %BW	-5.0*	-6.6*
$\Delta[HCO_3^-]_e$, mEq/L	-4.3*	-4.3*
$\Delta[H^+]_e$, nEq/L	+9.3*	+9.7*
$\Delta[H^+]_i$, nEq/L	-43*	-39*
$[H^+]_i/[H^+]_e$	3.73 → 2.14*	3.10 → 1.85*

Makoff, Da Silva, Rosenbaum, 1970

A second possible mechanism is that shown in Figure 11b. Once again, hypertonic infusions lead to cell shrinkage with shift of volume from the intracellular compartment to the extracellular compartment. In addition to effects on intracellular potassium concentration, there are also effects on intracellular and extracellular pH. Shift of water out of cells will concentrate bicarbonate within cells and dilute bicarbonate in the extracellular fluid. Because CO_2 is freely permeable, there will be no effects on pCO_2. Thus, this will lead to an expansion acidosis in the extracellular fluid and a contraction alkalosis in the intracellular fluid. As shown in the data of Mackoff et al (21), this causes a marked decrease in the ratio of the hydrogen ion concentrations in the intracellular to the extracellular fluid. Based on our previous discussion, this would then be expected to lead to a potassium shift into the extracellular fluid. At present, it would seem that the most likely explanation is a combination of the above two mechanisms. The relative importance of these mechanisms remain unclear presently. While investigators have attempted to dissociate the K shift seen with hypertonic infusions from the hydrogen gradients, they have not convincingly excluded a role for such a mechanism (22).

It is important to note that this K shift can be seen in the absence of hypertonic infusates, and merely requires a shift of water out of cells. For instance, infusion of isotonic mannitol which is unable to enter cells will cause a small shift of water outside of cells without causing detectable hypertonicity in patients. Moreno et al (20) showed that such an infusion will lead to a potassium shift out of the cell. As will be discussed below, this is important with respect to understanding K shifts in diabetic patients.

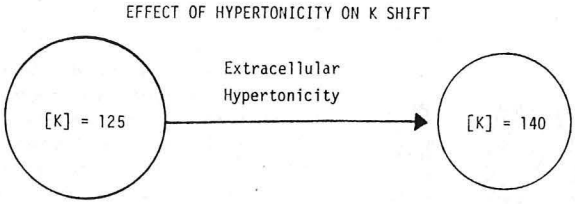


FIGURE 11a

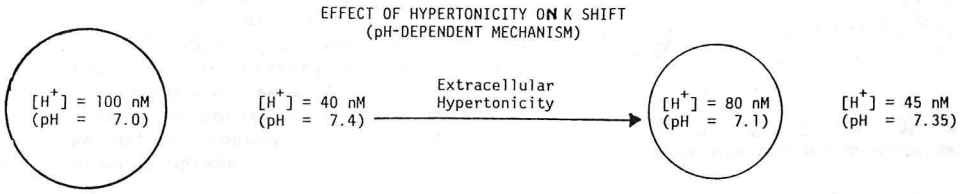


FIGURE 11b

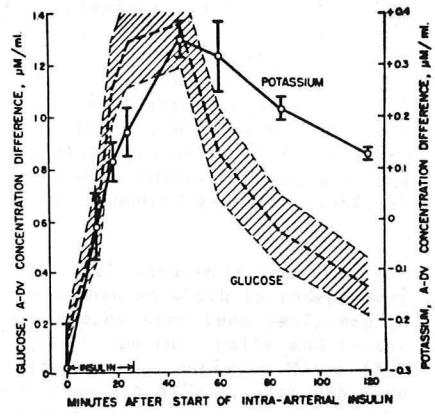
Increases in serum glucose accompanied by decreases in serum sodium such that plasma osmolality is normal, will still lead to shifts of potassium outside of cells.

ROLE OF INSULIN

Another factor which has been demonstrated to have a major effect on K shifts is insulin. Harrup and Benedict (23) and Briggs and Koechig (24) first reported in 1923 and 1924 respectively that insulin injection into patients was associated with a decrease in plasma potassium concentration. This observation remained unexplained until Zierler (25) in 1959 demonstrated that insulin caused cell hyperpolarization in an isolated muscle preparation. This was associated with a probable increase in cell potassium content. Interestingly, Zierler (25,26) showed that this effect could be demonstrated in the total absence of glucose, and postulated that insulin could affect potassium uptake by cells by a glucose-independent mechanism.

In order to demonstrate this, Andres et al (27) utilized the technique of human forearm perfusion. With this technique a double lumen needle is inserted into the brachial artery, one lumen for sampling and a second for infusions. A polyethylene catheter is then threaded into an antecubital vein and passed distally so that it samples blood draining the deep muscle of the forearm. Blood flow is measured by indicator dilution techniques. Glucose and potassium uptake by the forearm can then be calculated using the measured blood flow rate and concentration differences between the artery and vein. Different concentrations of insulin can be achieved by infusion into the brachial artery.

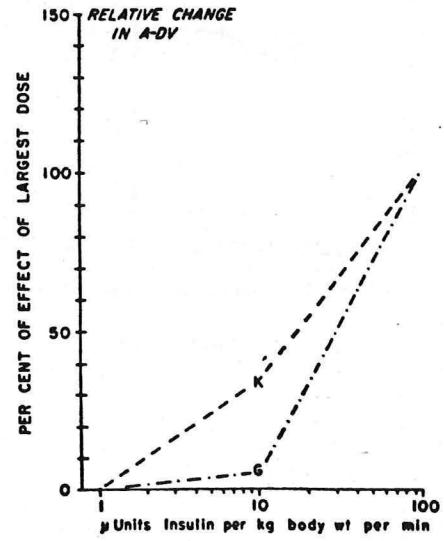
Figure 12 shows the results of initial studies by Andres and co-workers (27) where insulin was infused into the forearm for 25 minutes. The A-V concentration difference for glucose and potassium are shown. It can be seen that insulin caused an increase in both glucose and potassium uptake. However, the effect on potassium uptake peaked later and took longer to decay than the effect on glucose uptake. Based on these findings and the previous findings of Zierler (25,26), the authors concluded that insulin effects on glucose and potassium were separate, and that the effect on potassium was not merely a secondary consequence of increased glucose uptake.



Andres, Baltzan, Cader, and Zierler, 1962

FIGURE 12

In the previous studies, large concentrations of insulin were used. In subsequent studies, Zierler and Rabinowitz (28) examined the effect of lower concentrations of insulin on the arterial deep venous concentration differences for glucose and potassium. The dose response results are shown in Figure 13. Infusion of insulin at a rate of 1 microunit/kg BW/minute had no effect on the A-V difference of these two compounds. Insulin infused at 10 microunits/kg BW/minute, sufficient to raise brachial artery plasma insulin concentration by an average of 38 microunits/ml, markedly increased potassium uptake by forearm tissues with no demonstrable effect on glucose uptake. Higher rates of infusion then affected potassium and glucose uptake. Once again, these results suggest that the effect of insulin on potassium uptake in muscle is direct and not attributable to a secondary effect of increased glucose uptake.



Zierler and Rabinowitz, 1964

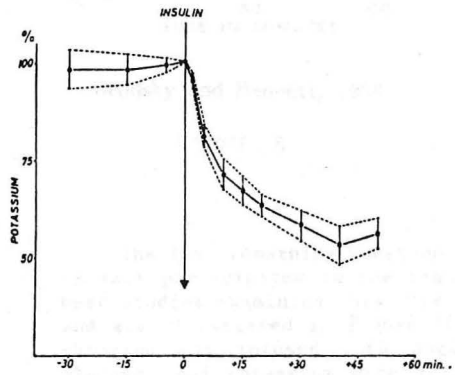
FIGURE 13

Kestens and co-workers (29) examined the effect of insulin on uptake of potassium and glucose in the cyclicly perfused dog liver. The results of these studies are shown in Figures 14a and 14b. When insulin was added to the perfusate, there was a rapid decrease in potassium concentra-

tion of the perfusate, signifying potassium uptake by hepatocytes (Figure 14a). In contrast, insulin did not affect glucose concentration of the perfusate implying no effect on glucose uptake. These studies were not performed to examine whether insulin affects glucose uptake in the liver. Rather, they show that insulin can stimulate potassium uptake in a setting where there is no effect on glucose uptake.

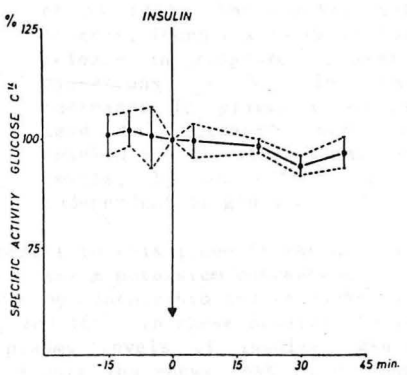
DeFronzo and co-workers (30) examined this question using the insulin clamp in human subjects. They found that increasing plasma insulin concentrations lowered plasma potassium concentration, and increased the rate of potassium uptake across the splanchnic circulation. Insulin also increased glucose uptake. However, whereas 70% of insulin-induced K uptake was splanchnic and presumably hepatic, most of insulin-induced glucose uptake was extra-splanchnic, and presumably muscle.

Thus, in summary, these data demonstrate that insulin causes the net movement of K into muscle and liver cells by a mechanism which is independent of its effect on glucose transport. Numerous studies have been performed to examine the mechanism by which insulin moves potassium into cells and causes cell hyperpolarization. This data has been reviewed recently by Moore (31) and is most consistent with an effect of insulin on NaK ATPase, although some question remains as to whether the effect is direct.



Kestens, Haxhe, Lambotte, and Lambotte, 1963

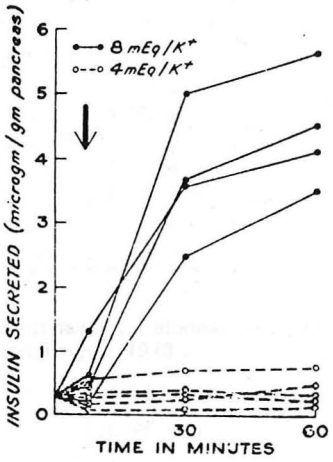
FIGURE 14a



Kestens, Haxhe, Lambotte, and Lambotte, 1963

FIGURE 14b

EFFECT OF K^+ ON INSULIN SECRETION IN ABSENCE OF GLUCOSE



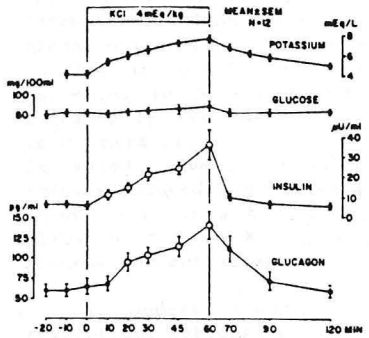
Grodsky and Bennett, 1966

FIGURE 15

The next question is whether increases in serum potassium concentration lead to insulin release. This has been studied in the intact animal where plasma insulin concentrations have been measured and found to increase in response to potassium infusion (32-35). In addition, insulin secretion by the isolated perfused pancreas has been studied in response to changes in the potassium concentration of the perfusate. Figure 15 shows the results of Grodsky and Bennett (36). Increasing perfusate potassium concentration from 4 to 8 mEq/liter caused an increase in insulin secretion. This effect required the presence of calcium but could be demonstrated in the complete absence of glucose. Similar results have been reported by Gomez and Curry (37) and Kuzuya et al (38). These investigators, however, found a more rapid insulin release in response to sustained elevations in K. In summary, increases in plasma potassium do lead to increased secretion of insulin and elevated plasma insulin levels, by an effect which is independent of glucose.

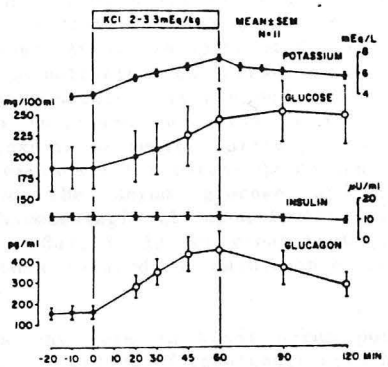
The last remaining question with respect to this issue is whether insulin in fact participates in the regulation of serum potassium concentration. The best studies examining this were performed by Santeusanio and co-workers (35), and are illustrated in Figure 16a, 16b, and 16c. In these studies, potassium chloride was infused into dogs and plasma levels of insulin, glucagon, glucose, and potassium were followed. Figure 16a shows that in response to KCl infusion, there was an increase in serum potassium concentration and in plasma levels of insulin and glucagon. Serum glucose concentration was unaffected. Figure 16b shows the results of similar experiments performed in dogs made diabetic by alloxan treatment. It can be noted that the potassium infusion used was smaller in magnitude. This is because the potassium infusion used in normal dogs caused much greater increases in serum potassium concentration in the diabetic dogs and was fatal. In diabetic dogs, the smaller potassium infusion was associated with an increase in glucagon levels and an increase in serum glucose concentration, most likely secondary to the increase in glucagon secretion. These studies demonstrate that insulin plays a physiologic role in the defense of serum potassium concentration after a potassium load. Animals deficient in insulin are unable to tolerate the same K load that a normal dog can tolerate.

ALLOXAN-TREATED DOGS



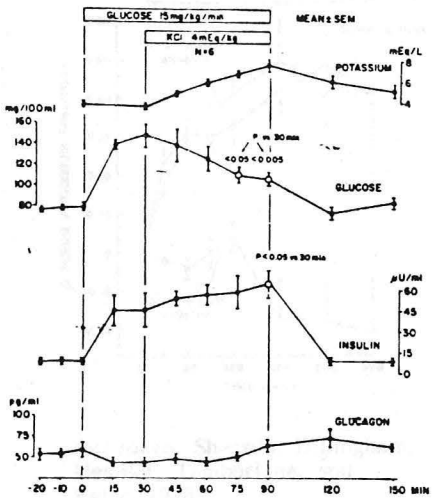
Santeusanio, Faloona, Knochel, and Unger, 1973

FIGURE 16a



Santeusanio, Faloona, Knochel, and Unger, 1973

FIGURE 16b

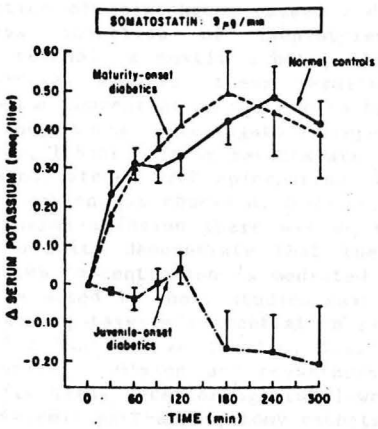


Santeusanio, Faloona, Knochel, and Unger, 1973

FIGURE 16c

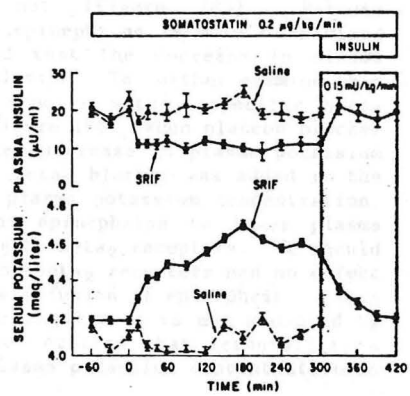
The studies in Figure 16c were performed to examine the role of glucagon in the response to a KCl infusion. In these studies an infusion of glucose was used to suppress glucagon secretion. Then, a KCl infusion was started. The KCl caused an increase in insulin secretion but was unaccompanied by increased glucagon secretion in these experiments. In spite of this defect in glucagon secretion, the increment in serum potassium concentration was similar to that in normal dogs. Thus, from these studies, it can be concluded that increases in potassium intake lead to increased secretion of insulin and glucagon by the pancreas. Increased insulin secretion shifts part of the K load intracellularly and thus defends extracellular potassium concentration. Increased levels of glucagon defend the serum glucose and prevent insulin-induced hypoglycemia. While pharmacologic glucagon levels have been shown to cause a K shift out of cells (38a), it is not clear that glucagon plays a role in K regulation other than related to maintenance of serum glucose concentrations.

To address whether insulin plays any role in basal serum potassium regulation, DeFronzo et al (39) examined the effect of somatostatin, a hormone which inhibits insulin secretion, on serum potassium concentration. Figure 17a shows the response of serum potassium in three groups of patients. In normal controls and patients with maturity onset diabetes, both groups of which have somatostatin-suppressible insulin secretion, there was an increase in serum potassium concentration. However, in patients with juvenile onset



DeFronzo, Sherwin, Dillingham, Hendler, Tamborlane, and Felig, 1978

FIGURE 17a



DeFronzo, Sherwin, Dillingham, Hendler, Tamborlane, and Felig, 1978

FIGURE 17b

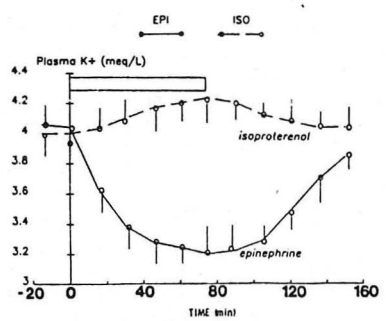
diabetes who have no insulin and thus are unaffected by somatostatin, this increase in serum potassium concentration did not occur. Similar studies performed in dogs are shown in Figure 17b. Here it can be seen that somatostatin infusion suppressed plasma insulin levels and increased plasma potassium concentration. Both effects were reversed by insulin infusion. These studies demonstrate that insulin participates in the regulation of basal potassium concentration. Decreased insulin levels as would occur with somatostatin infusions or in patients with diabetes, are thus able to lead to a relative shift of potassium outside of cells and higher plasma potassium levels. In addition, these patients will be more susceptible to increases in plasma potassium concentration in response to exogenous potassium loads.

ROLE OF CATECHOLAMINES

Before discussing the clinical relevance of these potassium shifts, I would like to pursue one more modulator of potassium movement between compartments, that of catecholamines. D'Silva (40) first demonstrated that intravenous administration of adrenalin caused a rapid rise in plasma potassium concentration which was followed after a few minutes by a fall below normal levels. Subsequent studies by Todd and Vick (41) found that the initial rise in K was blocked by phenoxybenzamine, an alpha blocker, while propranolol, a beta blocker, blocked the subsequent fall in plasma potassium concentration. These results suggest that alpha adrenergics cause potassium to move out of cells and beta adrenergic catecholamines cause potassium to move into cells.

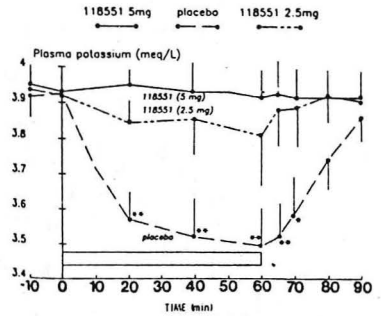
Figure 18 shows more recent studies by Brown, Brown, and Murphy (42) where the effect of beta catecholamines was examined. These studies show that injection of epinephrine caused a decrease in plasma potassium concentration whereas injection of isoproterenol did not (Figure 18a). Because isoproterenol is mostly a $beta_1$ agonist, and epinephrine is more of a mixed $beta_1$-$beta_2$ agonist, these results suggested that the decrease in plasma potassium concentration was due to $beta_2$ stimulation. To further examine this question, these investigators repeated the studies with a specific $beta_2$ blocker, 118551. These results are shown in Figure 18b. When placebo blocker was administered with epinephrine, the expected decrease in plasma potassium concentration was observed; however, when the $beta_2$ blocker was added to the epinephrine infusion there was no change in plasma potassium concentration. These results demonstrate that the effect of epinephrine to lower plasma potassium concentration is mediated by binding to $beta_2$ receptors. It should also be noted in these studies that blockade of $beta_2$ receptors had no effect on plasma potassium concentration prior to the infusion of epinephrine. This suggests that unlike insulin, basal potassium regulation is not mediated by epinephrine. Olsson and co-workers (43) also reported that terbutaline, a specific $beta_2$ receptor agonist lowered the plasma potassium concentration in hyperkalemic post-nephrectomy rabbits.

To examine the mechanism of this effect, Clausen and Flatman (44,45) studied the effect of various catecholamines on NaK ATPase in rat soleus muscle. They found that adrenalin stimulated NaK ATPase, and that while propranalol, a non-specific beta blocker, blocked the effect, metoprolol, a specific $beta_1$ blocker, was much less potent. In addition, salbutamol, a $beta_2$ agonist, caused activation of the NaK ATPase.



Brown, Brown, and Murphy, 1983

FIGURE 18a



Brown, Brown, and Murphy, 1983

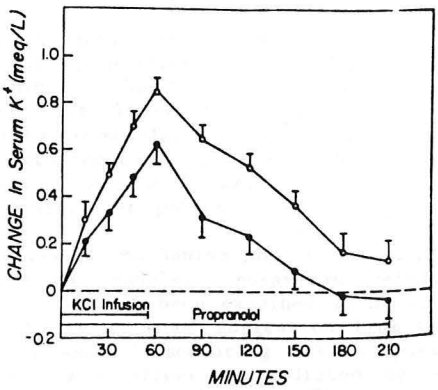
FIGURE 18b

Beta$_2$ receptors have been shown to mediate the catecholamine effects of bronchodilation and vasodilation, with little effect on cardiac stimulation and lipolysis (46). It is thus tempting to speculate that the effect of beta$_2$ receptors on serum potassium concentration and on decreasing smooth muscle tone are similar. Indeed, Scheid, Honeyman, and Fay (47) found that beta$_2$ adrenergic smooth muscle relaxation was dependent on cyclic AMP-dependent phosphorylation and enhanced NaK ATPase. The enhanced NaK ATPase would enhance Na-Ca exchange, lowering intracellular calcium concentration and causing smooth muscle relaxation. In addition, enhanced NaK ATPase activity would cause a shift of potassium from the extracellular fluid to the intracellular fluid. While beta$_2$ stimulated shifts of potassium into smooth muscle cells probably occurs, it is likely that the majority of the potassium shift in the body occurs due to similar mechanisms in skeletal muscle, as shown by Clausen and Flatman (44,45). Whether there are any specific effects of NaK ATPase stimulation on skeletal muscle function has not been examined.

In order for catecholamines to provide an important mechanism for regulation of serum potassium concentration, it is also necessary for extracellular fluid potassium concentration to affect catecholamine secretion. This has been found in the denervated cat adrenal gland with KCl perfusion (48), in the in vitro perfused bovine adrenal gland (49,50), and in adrenal slices (49). Baker and Rink (49) found that increasing the potassium concentration of the extracellular fluid caused adrenal glands to depolarize which activated calcium channels. They postulated that increased cell calcium concentrations caused exocytosis and catecholamine secretion.

Numerous investigators have done studies to document the importance of beta catecholamines in the defense of extracellular fluid potassium concentration after a K load. Figure 19 shows the results of Rosa and colleagues (51) who performed KCl infusions into human subjects and examined the increase in serum potassium concentration. Whereas propranolol had no effect on basal potassium concentration, propranolol addition markedly enhanced the KCl induced increase in serum potassium concentration. These studies demonstrate that KCl infusion leads to beta catecholamine secretion of sufficient magnitude to defend serum potassium concentration. Blockade of beta receptors prevents this effect. Numerous other investigators have found similar results

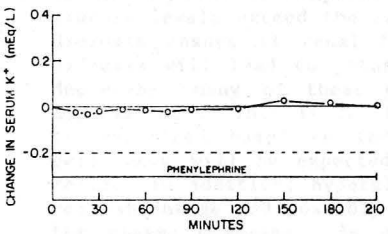
(52-55). Bia et al (53) examined the response to KCl infusion in nephrectomized rats. Adrenalectomy impaired serum potassium defense, and this was corrected by epinephrine. DeFronzo et al (52) also found in humans that addition of propranolol to KCl infusion enhanced the increment in plasma potassium concentration. Silva et al (54) found that depletion of catecholamine by prior treatment with 6-hydroxydopamine in nephrectomized adrenalectomized rats increased the potassium increment to a K load, suggesting an effect of extra-adrenal catecholamines. Lastly, Tyler et al (55) found that the increment in plasma potassium concentration induced by a K infusion in rats was decreased by epinephrine or terbutaline, a $beta_2$ agonist, increased by propranolol or butoxamine, a $beta_2$ blocker, and not affected by metoprolol, a $beta_1$ blocker.



Rosa, Silva, Young, Landsberg, Brown, Rowe, and Epstein, 1980

FIGURE 19

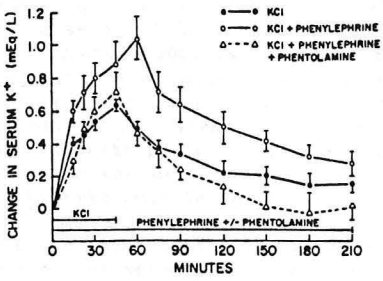
Thus, in summary, it appears that while $beta_2$ catecholamine receptors do not participate in basal potassium regulation, they are important components in the defense against a potassium load. Increases in potassium intake lead to increased catecholamine secretion. Catecholamines, by binding to $beta_2$ receptors, cause enhanced potassium uptake by muscle. This modulates the increase in plasma potassium concentration. This effect of catecholamines cannot be explained by renal actions as it has been found in nephrectomized animals (53-55), and when urine K excretion has been measured it has not explained the effect (52).



Williams, Rosa, Silva, Brown, and Epstein, 1984

FIGURE 20a

Attention has also recently been raised toward regulation of serum potassium by alpha catecholamine receptors. Williams and coworkers (56) examined the role of alpha receptors on potassium regulation in the basal state and after a potassium load in humans. As shown in Figure 20a, infusion of phenylephrine, an alpha agonist, in low concentrations such that blood pressure was unaffected, had no effect on serum potassium concentration. In addition, blockade of alpha receptors with phentolamine had no effect on serum potassium concentration. These studies demonstrate that alpha catecholamines are unable to affect basal potassium regulation. Figure 20b demonstrates the response to potassium infusion. In this setting, addition of phenylepherine to the



Williams, Rosa, Silva, Brown, and Epstein, 1984

FIGURE 20b

infusion enhances the rise in potassium concentration, an effect which is blocked by phentolamine. Thus, in response to a potassium load, alpha catecholamines develop the ability to modulate the serum potassium. In these studies this effect was shown not to be mediated by the kidneys, and thus to involve shifts of potassium out of cells.

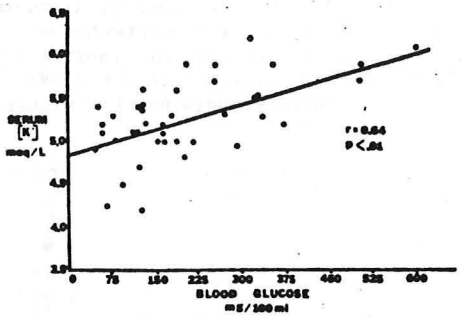
The exact mechanism by which alpha catecholamines modulate potassium release from cells has not been examined in detail. However, there is some suggestion from the studies of Akaiki, measuring cell composition, that the effect is mediated by an inhibition of the NaK ATPase. The data of Williams and co-workers (56) suggest that alpha catecholamines would have no effect on NaK ATPase under basal conditions but rather would modulate the response to a K load. One possible explanation for these results would be if alpha catecholamines stimulated an inhibitory receptor on the adenylate cyclase, which modulated the effect of $beta_2$ catecholamines on the adenylate cyclase. Under basal conditions, as discussed above, $beta_2$ activation can shift potassium into cells but does not, presumably due to low catecholamine levels. In this setting, alpha catecholamines would have no effect. However, after a K load $beta_2$ and alpha catecholamines would be released, with alpha catecholamines modulating the response of the NaK ATPase to $beta_2$ stimulation.

CLINICAL RELEVANCE OF EXTRARENAL POTASSIUM REGULATION

Diabetes, Ketoacidosis, Hyperglycemia

As presented in the introduction to this manuscript, potassium regulation in ketoacidosis is complex. When diabetes is out of control, such that serum glucose levels exceed the renal threshold for glucose absorption, an osmotic diuresis ensues if renal function is intact. In all patients, an osmotic diuresis will lead to potassium depletion. However, in spite of potassium depletion, many of these patients are not hypokalemic and some are even hyperkalemic. This is due to a shift of potassium out of cells which can now be explained based on the above discussion. On the one hand, insulin deficiency will be expected to cause a relative shift of potassium out of cells. In addition, hyperglycemia will cause a K shift out of cells, due to cell shrinkage and possibly due to secondary creation of pH gradients across the plasma membrane. As discussed extensively above, it is unlikely that ketoacidosis per se is responsible for potassium shifts out of cells. When the patient is then treated with insulin, these factors are reversed. The presence of insulin will rapidly stimulate the NaK ATPase and lead to potassium shift into cells. In addition, as serum glucose decreases, the cells will swell and potassium will be returned to the intracellular compartment.

These determinants of K shifts are not only relevant to patients with ketoacidosis and hyperosmolar states, but are also relevant to patients with diabetes in general. Random decreases in insulin levels and increases in glucose levels may potentially lead to oscillations in the serum potassium. Administration of glucose to these patients can paradoxically lead to an increase in serum potassium (58-62). The reason that this is paradoxical is that glucose administration to normal subjects is associated with increased insulin secretion and a secondary decrease in serum potassium. In non-diabetic patients, glucose administration can be used in the treatment of hyperkalemia to shift K into cells. In some diabetic patients, however, glucose administration paradoxically raises the serum potassium. This most likely occurs because of a failure of insulin to be secreted combined with cell shrinkage secondary to the increased plasma glucose. In addition, Goldfarb and co-workers have shown that if serum potassium and serum glucose are followed over time in some patients there is an excellent correlation between them with potassium increasing as glucose increases (Figure 21).



Goldfarb , Strunk, Singer, and Goldberg, 1975

FIGURE 21

This effect of glucose on potassium has been seen most frequently in diabetics with hyporeninemic hypoaldosteronism (58-60). This renal lesion which causes an impairment in potassium excretion most likely helps to bring out the defect in cell membrane potassium transport. Glucose induced hyperkalemia, however, has also been reported in patients with normal aldosterone levels (61,62).

Lactic Acidosis

As referred to above, K shifts have frequently been observed in patients with lactic acidosis. This observation has helped to foster the belief that organic acidoses lead to potassium shifts. While studies have demonstrated that lactic acidosis associated with seizures is not associated with potassium shifts out of cells (7,8), lactic acidosis associated with shock certainly is associated with potassium shifts out of cells (62a). Sayeed (62a) has recently reviewed this area and presented evidence which shows that shock is associated with failure of the NaK ATPase which leads to net shift of potassium out of cells. Thus, as with diabetic ketoacidosis, patients with lactic acidosis have a shift of K out of cells which accompanies the lactic acidosis but is not caused by it.

Potassium Load

As discussed at the beginning of this manuscript, large potassium loads, whether oral or intravenous, require extrarenal handling prior to renal excretion. While it is possible that increased plasma potassium concentration per se enhances net potassium movement into cells, it appears that the bulk of this regulation is mediated by two hormonal systems, as shown in Figure 22. Increases in extracellular potassium concentration lead to an increase in secretion of insulin, glucagon, and epinephrine. Insulin and epinephrine lead to enhanced potassium uptake, most likely by stimulation of NaK ATPase. Enhanced glucagon secretion prevents insulin-induced hypoglycemia.

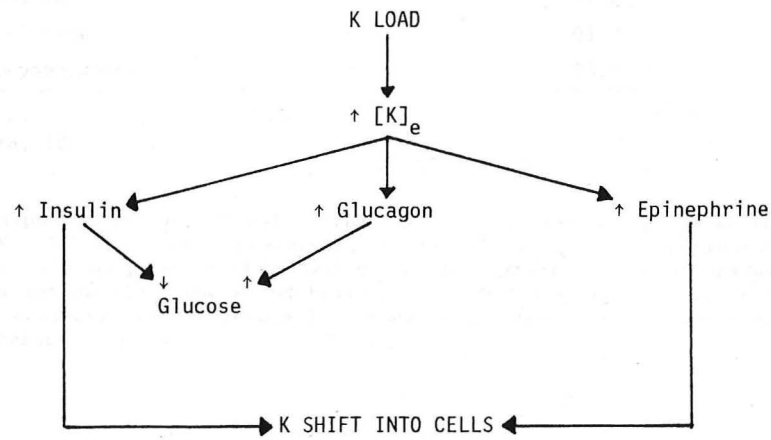


FIGURE 22

Potassium Deficiency

As the body becomes potassium depleted, there is a shift of potassium from the intracellular compartment to the extracellar compartment to defend serum potassium concentration. This shift occurs mostly out of skeletal muscle. Akaike (57) demonstrated that skeletal muscle from a potassium-deficient rat had a low intracellular potassium concentration and a high intracellular sodium concentration, consistent with inhibition of the the NaK ATPase. He found that if he removed the muscle from the rat and incubated it in low potassium containing medium, the cells rapidly accumulated potassium and extruded sodium, implying that the extracellular potassium concentration was not limiting potassium uptake. The results of his studies are shown in Table 8. Akaike found that denervation of the muscle caused intracellular sodium and potassium to return to normal, implying a neurogenic inhibition of the NaK ATPase. While propranolol did not mimic this effect, three alpha blockers, dibenamine, phentolamine, and phenoxybenzamine, all mimicked the effect of denervation. These studies demonstrate that in potassium deficiency

TABLE 8

INTRACELLULAR [Na] AND [K] IN POTASSIUM DEFICIENCY

	$[Na]_{cell}$	$[K]_{cell}$
Control	73.3	75.4
Denervation	36.8	113.1
Propranolol	71.1	78.3
Dibenamine	48.7	97.2
Phentolamine	50.7	91.2
Phenoxybenzamine	49.0	93.7

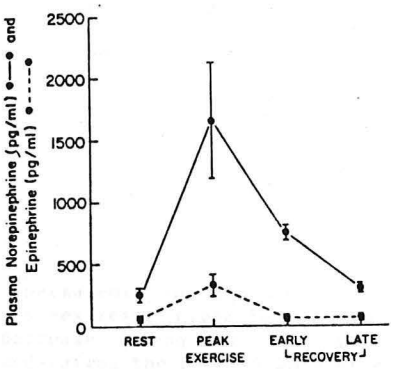
Akaika, 1981

there is an alpha adrenergic stimulus from the central nervous system which inhibits NaK ATPase, and preserves extracellular fluid potassium concentration. The purpose of this system is to maintain normal potassium concentrations for cardiac muscle and brain. It is interesting to note that CSF potassium concentration is generally preserved in potassium deficiency by the choroid plexus.

Exercise

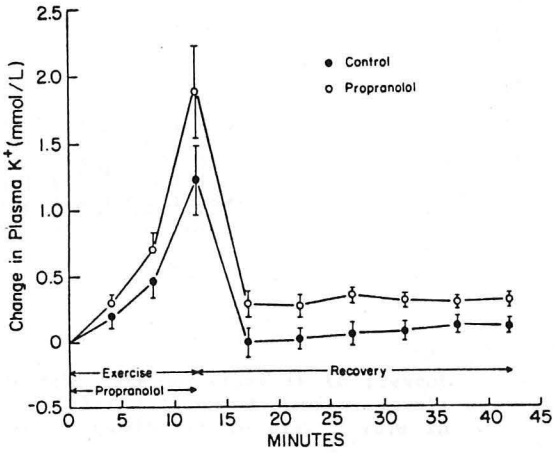
Williams and co-workers (63) have performed interesting studies examining the effect of exercise on serum potassium concentration. As shown in Figure 23a, when human subjects are exercised, there is an increase in plasma levels of norepinephrine and epinephrine during exercise. Whereas epinephrine levels return to normal during early recovery, norepinephrine levels remain elevated for a longer time. Williams et al examined the effect of alpha and beta blockade on the pattern of serum potassium concentration during exercise. Figure 23b shows the effects of beta blockade with propranolol. As can be seen, beta blockade caused a larger increase in serum potassium concentration during exercise which persisted in the post-exercise period. These results imply that during exercise beta catecholamine release is responsible for stimulating potassium uptake and thus modulates the potassium release from muscle.

Figure 23c shows the response to alpha receptor blockade by phentolamine. As can be seen, alpha blockade causes a lower peak plasma potassium level during exercise and then leads to a post-exercise hypokalemia. Thus, alpha adrenergic stimulation during exercise enhances potassium movement from muscle, enhances hyperkalemia during exercise, and prevents post-exercise hypokalemia. Putting this data together it appears that the role of beta adrenergic catecholamines during exercise is to modulate the degree of



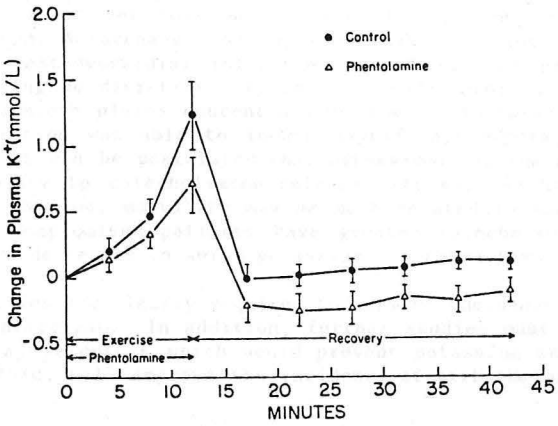
Williams, Gervino, Rosa, Landsberg, Young, Silva, and Epstein, 1985

FIGURE 23a



Williams, Gervino, Rosa, Landsberg, Young, Silva, and Epstein, 1985

FIGURE 23b

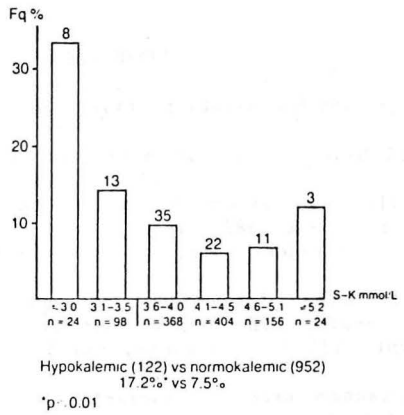


Williams, Gervino, Rosa, Landsberg, Young, Silva, and Epstein, 1985

FIGURE 23c

FIGURE 24

(Nordrehaug, 1985)



hyperkalemia and the role of alpha adrenergic catecholamines is to prevent post-exercise hypokalemia. Bottger et al (63a) found that insulin levels decrease during exercise, and thus insulin appears not to play a role in moderating the hyperkalemia of exercise.

Myocardial Infarction and the Risk of Hypokalemia

Numerous investigators have now reported that hypokalemia increases the incidence of supraventricular and ventricular arrhythmias in the immediate post-myocardial infarction period (Figure 24) (64-67). While a fraction of this hypokalemia can be attributed to thiazides, most series find a significant proportion of patients who are hypokalemic in the immediate post-infarction period yet have no history of thiazide or other diuretic ingestion. Indeed, Nordrehaug (64) reported that potassium levels continued to drop in the post-myocardial infarction period in some patients, some of whom were receiving no diuretics. Brown et al (42) reported that infusion of epinephrine to achieve plasma concentrations similar to those achieved during myocardial infarction was able to induce significant hypokalemia. Based on these findings, it can be postulated that hypokalemia in the post- infarction period is secondary to catecholamine release. If so, the high incidence of arrhythmias and the poor mortality may be more related to the fact that more hemodynamically compromised patients have greater catecholamine release and greater secondary decreases in serum potassium concentration.

Further studies are clearly required to examine the danger of hypokalemia in myocardial infarction. In addition, further studies must examine whether blockade of $beta_2$ receptors which would prevent potassium shifts out of the extracellular fluid, will improve the incidence of arrhythmias and mortality.

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