

Physiology and Pathophysiology of Transcellular Shift of Potassium Balance

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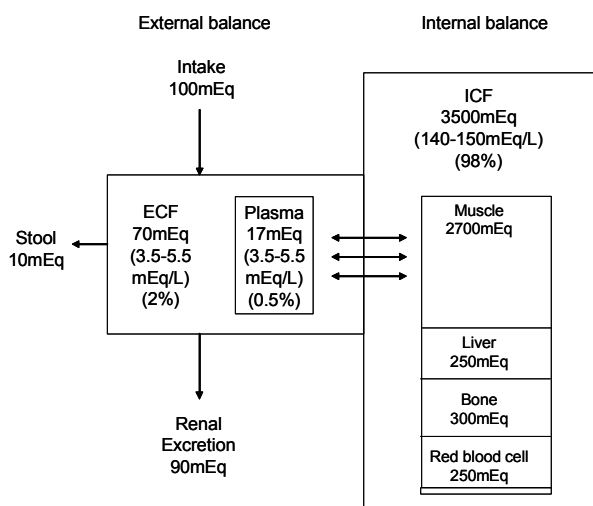
Plasma potassium level is maintained within a narrow normal range through a transcellular shift between intracellular and extracellular space, and through renal excretion. Internal potassium balance via transcellular shift is affected by several hormones and physiologic conditions. Catecholamine through β_2 -adrenergic receptor stimulates cellular uptake of potassium and defends against increments in plasma potassium concentration. Insulin promotes cellular potassium uptake in muscle, liver and adipose tissues. Changes of acid-base status affects internal potassium balance as well as renal potassium excretion. Other physiologic and pathophysiologic conditions such as exercise or tissue damage also have acute effects on the distribution of potassium. Although a lot of medications are the causes of hyperkalemia, drugs that alter internal potassium balance would appear to be uncommon. Understanding the physiology of potassium distribution is important to evaluate and manage the patients with potassium disturbances including hypokalemia or hyperkalemia.

Key Words: Internal potassium balance, Catecholamine, β_2 -adrenergic receptor, Insulin, Na,K-ATPase, Acid-base, Organic acid, Hypertonicity

The kidney plays a major role in maintaining the homeostasis of potassium by regulating its excretion. However, nonrenal tissues including muscle and liver, are also important organs in the regulation of potassium balance. The regulation of potassium distribution between intracellular and extracellular space in nonrenal tissues are defined as internal potassium balance.

The total body potassium stores in a 70-kg normal adult are 3,500 mEq (Fig. 1). Potassium is basically an intracellular cation with 140 to 150 mEq/L concentration, 98% of body potassium being located in the cells. The largest fraction of intracellular potassium is located in skeletal muscle, which contains 2,700 mEq. The rest portion of intracellular potassium is in red blood cells, liver and bones. The remaining 2% of total body potassium is located in extracellular space, where the normal concentration is 3.5 to 5.5

mEq/L. Thus, a large chemical concentration gradient exists for potassium to diffuse from the cells into the extracellular space. Because cell membranes have a restricted permeability to potassium, an equilibrium must exist between the intracellular and extracellular



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Fig 1. Internal potassium balance in a 70-kg adult. re-drawn from Rosa RM, Epstein FH: External potassium metabolism, in *The Kidney: Physiology and Pathophysiology*, edited by Seldin DW, Giebisch G, Philadelphia, JB Lippincott Company, 2000, p1551-1573

spaces. This equilibrium represents a steady-state where the efflux of potassium from cells is nearly matched by an influx of potassium into the cells. Potassium efflux from cells occur via potassium channels. In contrast, cellular influx of potassium depends on the activity of the sodium-potassium adenosine triphosphatase (Na,K-ATPase) pump, located in the plasma membranes of cells.

Potassium has two important physiologic functions. First, it plays a major role in cellular metabolism, such as protein and glycogen synthesis. Second, the ratio of the potassium concentration in the intracellular and the extracellular space is the major determinant of the resting membrane potential. The resting membrane potential sets the stage for the generation of the action potential that is essential for normal neural and muscular function.

The major factors that regulate internal potassium balance are hormones such as insulin and catecholamine, acid-base status, and plasma tonicity. In the daily regulation of internal potassium balance, only insulin and catecholamines play an important role in maintaining the normal distribution between intracellular and extracellular fluid compartments. However, the disturbances of acid-base status and plasma osmolality under pathophysiologic conditions can have profound effects on the plasma potassium concentration.

Most factors affecting internal potassium balance have critical roles in mitigating potentially dangerous changes in the concentration of plasma potassium. Disorders of those factors may have serious clinical problems. In this paper, physiologic and pathophysiologic conditions of internal potassium balance will be briefly reviewed.

Catecholamine

Epinephrine was demonstrated to stimulate both α - and β -adrenergic receptors over 50 years ago. The fact that stimulating effect of catecholamine on

potassium uptake is mediated by β_2 -receptor subtype was established by studies using agonists and antagonists¹. β_2 receptor stimulation initiates cAMP formation by stimulating adenylate cyclase, which leads to activation of Na,K-ATPase and electrogenic sodium efflux accompanied by potassium influx². β_1 -adrenergic agonists do not affect potassium metabolism by extrarenal tissues¹. Williams et al. tested the effect of α -adrenergic nervous system on the extrarenal potassium disposal in healthy human³. Administration of a pure α -agonist phenylephrine augmented the rise of plasma potassium concentration, but the addition of the α -antagonist phentolamine blocked the rise in plasma potassium level induced by phenylephrine (Fig. 2). From these results, it was demonstrated that the stimulation of α -receptors impairs extrarenal potassium disposal of an acute potassium load—the opposite effect of β_2 -adrenergic stimulation. The cellular mechanism of α -adrenergic receptor to potassium distribution is its impairment of potassium uptake into the cell.

Endogenous catecholamines act to defend against increments in extracellular potassium concentration. Two most common circumstances are feeding and exercise. Feeding stimulates the sympathetic nervous

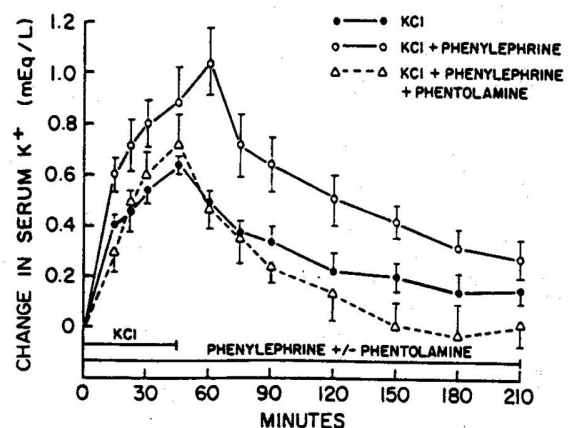


Fig. 2. Effect of simultaneous phenylephrine and phentolamine on the increment in serum potassium induced by an intravenous KCl load adapted from Williams ME, Rosa RM, Silva P, Brown RS, Epstein FH: Impairment of extrarenal potassium disposal by α -adrenergic stimulation. N Engl J Med 311:145-149, 1984

system, which limits the elevations of serum potassium in immediate postprandial period⁴). During vigorous exercise, catecholamine circulates at high levels. The short-term elevation of potassium that is released into the circulation from working muscles can be exaggerated by β blockade (Fig. 3). This suggests that endogenous β -adrenergic activity does protect against extreme hyperkalemia during exhaustive exercise⁵).

Catecholamine are also important in certain pathophysiologic conditions. If the patient has been treated with propranolol, the increase of plasma potassium concentration after potassium load is exaggerated. This is due to a reduction in cellular potassium uptake in muscle and liver⁶). In a stressful condition such as acute myocardial infarction, release of epinephrine can lower the plasma potassium concentration. The frequency of hypokalemia during acute myocardial infarction has been observed to be 15% to 30%. In this condition, increased β_2 -adrenergic activity enhances insulin secretion by direct stimulation of pancreas and by enhancing glycolysis, leading to hypokalemia. Concomitant therapy with diuretics may further increase the frequency of hypokalemia during myocardial infarction⁷). Patients with asthma or heart failure usually have medication with β_2 -adrenergic

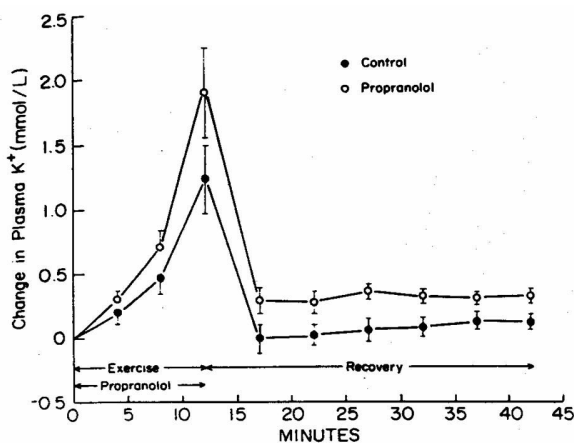


Fig. 3. Effect of propranolol on the rise and fall of plasma potassium during and after exercise adapted from Williams ME, Gervino EV, Rosa RM, Landsburg L, Young JB, Silva P, Epstein FH. Catecholamine modulation of rapid potassium shifts during exercise. *N Engl J Med* 312:823-827, 1985

agonist such as albuterol, dobutamine. A similar hypokalemic response can be induced in these patients.

Insulin

Insulin is the most important regulator of internal potassium balance and closes feedback loop that prevents hyperkalemia (Fig 4). Potassium directly stimulates insulin secretion by the pancreas from *in vitro* studies⁸). *In vivo* experiments, the infusion of KCl markedly aggravated the potassium tolerance in pancreatectomized animals but the infusion of insulin along with the KCl restored the tolerance to normal condition⁹). In human experiment, DeFronzo et al. observed that the infusion of somatostatin to inhibit basal insulin secretion increased plasma potassium by 0.5 to 0.7 mEq/L, and the infusion of insulin reversed potassium concentration to normal¹⁰). This experiment demonstrates that basal insulin secretion is a critical factor in maintaining the fasting plasma potassium concentration within normal range. Muscle, liver and fat are the major insulin-responsive tissues in humans. Many *in vitro* and *in vivo* studies have proved that insulin causes a net uptake of potassium by skeletal, cardiac muscle, and adipose tissue independent of its effect on glucose metabolism¹¹⁻¹³).

The cellular mechanisms through which insulin

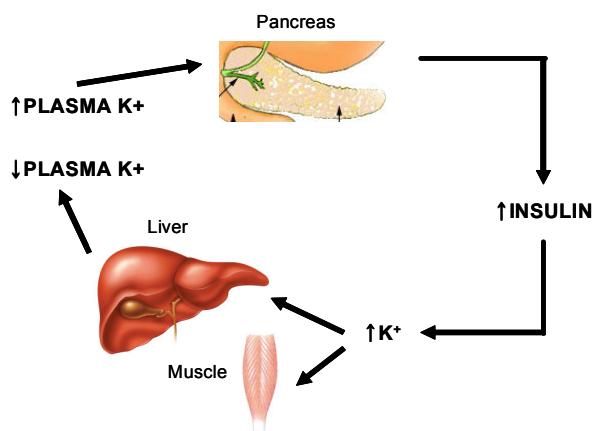


Fig. 4. Feedback loop relating changes in plasma potassium concentration to changes in insulin secretion by the beta cell.

enhances potassium uptake are illustrated in Fig. 2. Once insulin binds to its receptor, the cell membrane becomes hyperpolarized¹¹. This hyperpolarizing action of insulin results from a decrease in the ratio of sodium to potassium permeability and from a stimulation of Na,K-ATPase pump. The hyperpolarization results in the net cellular accumulation of potassium by passive distribution with the electrical gradient caused by sodium efflux. Activation of the Na,K-ATPase pump is related to the action of insulin to stimulate potassium transport. The second messenger that mediates this effect may be insulin receptor itself.

Glucagon

Glucagon mobilizes potassium from the liver and produces a transient rise in plasma potassium level. This response may be due to an epinephrine-like effect of glucagon to increase liver glycogenolysis¹⁴. Because glucagon also influences the secretion of insulin, epinephrine, and aldosterone, the effect of this hormone on the internal potassium balance is difficult to elucidate precisely. Systemic infusion of glucagon tends to elevate plasma potassium slightly, at least when glucagon-induced insulin secretion is suppress-

ed by somatostatin^{14, 15}.

Potassium content

Relationship between total body potassium and plasma potassium concentration is depicted in Fig. 5¹⁶. In the early phases of hypokalemia, there exists an almost linear relationship between body potassium and the plasma potassium concentration. In this phase the extracellular potassium concentration would be expected to fall proportionately more than the intracellular concentration, which may hyperpolarize cells⁷. When potassium depletion becomes more severe, a greater degree of potassium loss from the cells occurs than in the early phase of depletion. During potassium replacement for hypokalemia, cellular potassium uptake is enhanced¹⁸. As potassium content increases, the cellular uptake of potassium decreases and the concentration of plasma potassium tends to rise and the membrane potential decreases. In summary, the plasma potassium concentration varies directly with body potassium stores, decreasing with potassium depletion and increasing with potassium retention.

Acid-base

Although acid-base balance affects potassium excretion by the kidney, transcellular shifts of potassium are the initial way in which acid-base disturbances alter serum potassium. The relationship between pH and plasma potassium concentration is quite complex, and no single theory adequately explains all the reported changes in potassium concentration that occur during alterations in acid-base balance.

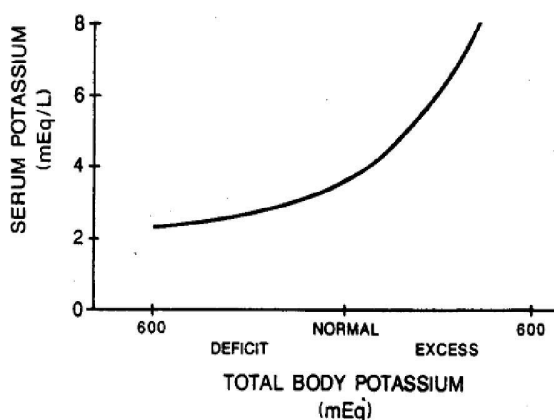


Fig. 5. Idealized relationship between the serum potassium concentration and the body potassium content adapted from Rosa RM, Epstein FH: External potassium metabolism, in *The Kidney: Physiology and Pathophysiology*, edited by Seldin DW, Giebisch G, Philadelphia, JB Lippincott Company, 2000, p1551-1573.

1. Hydrogen ion

Potassium exited from skeletal muscle *in vitro* when the bath pH was lowered and moved into the tissue when blood at physiologic pH was substituted

for acidic medium. Intracellular to extracellular ratio of hydrogen and potassium ions could be same according to Donnan equilibrium. Therefore, a decrease in that ratio produced by acidosis would be associated with a decrease in the ratio for potassium—that is, an increase in extracellular potassium. In metabolic acidosis, the excess hydrogen ions is buffered in the cells. Since the major extracellular anion chloride enters the cells only to a limited degree, electroneutrality is maintained by the movement of cellular potassium and sodium into the extracellular space¹⁹. Inhibition of Na,K-ATPase of plasma membrane by an acidic pH contributes to the relationship between acidosis and plasma potassium. Another mechanism might involve the link of Na,H antiporter and the Na,K-ATPase. Acidosis of the extracellular fluid would be expected to slow the rate at which hydrogen ions leave the cell and sodium ions enter, via Na,H antiporter. The resultant decrease in intracellular sodium concentration would slow the Na,K pump, reduce active uptake of potassium by cells, and increase the concentration of potassium in extracellular fluid²⁰. Intracellular acidosis appears to open ATP-sensitive potassium channels by reducing the degree of channel inhibition by ATP, which might accelerate efflux of potassium from the cells²¹.

2. Organic acids

In humans and animals, infusion of organic acids such as acetic, lactic, or β -hydroxybutyric acid produce much smaller elevations of potassium than does hydrochloric acid^{22, 23}. The anions of organic acids, by readily penetrating the intracellular compartment, by entering the cells as intact molecules, or by being formed endogenously within the cells, may minimize the necessity for potassium cations to leave the cells in exchange for hydrogen ions. Ketone acids stimulate the secretion of insulin by normal pancreas, while suppressing the secretion of glucagon. On the other hand, HCl do not stimulate insulin secretion but

enhance glucagon secretion²⁴. The activation of sympathoadrenal system, which is strongly activated in most clinical states accompanied by organic acidosis, plays an important role in minimizing hyperkalemia, because of the hypokalemic action of β -adrenergic stimulation²⁵.

The origin of potassium deficiency in diabetic ketoacidosis includes i) osmotic diuresis; ii) ketonuria, which obligates the excretion of cations to maintain electroneutrality; iii) hyperaldosteronism secondary to intravascular volume depletion; iv) intracellular phosphate loss, which is associated with potassium exit from the cell; v) insulin deficiency; vi) muscle catabolism associated with insulinopenia and high circulating levels of counterregulatory hormones; vii) decreased dietary potassium intake.

3. Respiratory acidosis

The effect of acute respiratory acidosis to elevate plasma potassium is smaller in magnitude than that of metabolic acidosis. This phenomenon is explained by the fact that carbon dioxide freely diffuses and remains intracellular, restraining potassium within the cell. In addition, it seems that sympathoadrenal stimulation plays a major role in modulating serum potassium during respiratory acidosis since it is well established that acute hypercapnia results in an intense sympathetic discharge and an increase in the plasma concentration of epinephrine¹⁹.

4. Bicarbonate

A decrease in plasma bicarbonate concentration, independent of changes in blood pH, also can influence the potassium concentration. If acid infuses to reduce bicarbonate concentration, but the arterial pH is maintained constant by simultaneous reduction of the $p\text{CO}_2$, the plasma potassium concentration still increases substantially²⁶. Moreover, bicarbonate administration reduces the plasma potassium level in hyperkalemic patients, even though blood pH remains constant²⁷. Bicarbonate corrects hyperkalemia directly

perhaps via intracellular transfer with the potassium cation. The factor that governs the release of intracellular potassium might be the quantity of acid buffered by cells rather than the arterial pH. That is, extracellular bicarbonate, rather than arterial pH, seems to control influence on extracellular potassium.

5. Alkalosis

In alkalosis, renal losses are important in initiating and perpetuating hypokalemia, but extrarenal adjustments are also involved. Acute alkalosis induced by infusions of sodium bicarbonate usually leads to a decrement in plasma potassium concentrations. Replacement of hydrogen ion associated with cellular buffers by potassium is a plausible explanation. Enhanced exchange of intracellular hydrogen for extracellular sodium via Na,H antiporter would accelerate cellular potassium accumulation by stimulating Na,K-ATPase pump.

Aldosterone

In addition to its action of renal potassium excretion, aldosterone enhances potassium secretion into intestinal fluids and saliva. Apart from this, there is no evidence for a direct action of aldosterone to increase potassium uptake by muscle cells. Using adrenalectomized dogs, Bia et al. demonstrated that for any given level of exchangeable potassium, the plasma potassium concentration was directly related to the aldosterone-replacement dose; the higher the plasma aldosterone concentration, the greater the amount of the total body potassium that resided within the cells²⁸). Aldosterone accelerates the extrarenal disposal of potassium, but probably not by a direct effect on muscle.

Exercise

With moderate to severe exercise, potassium is released from muscle cells. Muscle cells have ATP-

dependent potassium channels, where ATP reduces the number of open channels. Therefore, a reduction in ATP levels with marked exercise can open up more channels, thereby promoting potassium release from the cells²⁹). The local increase in the plasma potassium concentration has a vasodilatory effect that contributes to the enhanced blood flow to the exercising muscle. The hyperkalemia associated with exercise is generally mild and produces no symptoms. However, it can lead to a potentially dangerous elevation in the plasma potassium concentration in the presence of some other abnormality in potassium handling, such as exercise in persons with medication on β -adrenergic blocker.

Magnesium

In a variety of clinical states potassium depletion accompanies magnesium depletion. During magnesium depletion, the intracellular deficiency of potassium cannot be restored by provision of potassium alone; correction of the magnesium deficiency is required. Because Na,K-ATPase requires cellular magnesium, cellular potassium depletion due to diminished active potassium uptake by pump might occur³⁰). There is another mechanism of potassium loss by magnesium deficiency related to membrane potassium channels. Normally, intracellular magnesium blocks outward current by inhibiting the opening of ATP-sensitive potassium channels³¹). Such a direct effect of magnesium on potassium channels might result in cellular potassium depletion during magnesium deficiency.

Drugs

β blockers elevate potassium by impairing extrarenal disposal. Succinylcholine in patients with central nervous system diseases, spinal cord injury, can increase serum potassium to significant level, because of massive efflux of the cation from sensitized muscle³²). HMG-CoA reductase inhibitor may

cause muscle breakdown resulting hyperkalemia. Arginine HCl may increase serum potassium by taking up into cells and displacing potassium. Cardiac glycosides might induce hyperkalemia by blocking Na,K-ATPase-mediated potassium uptake. Hyperkalemia can be observed in lithium intoxication, because lithium displace intracellular potassium from human red blood cell and from skeletal muscle.

Insulin and β -adrenergic agonists induce hypokalemia. Theophylline increases circulating catecholamine levels and enhances catecholamine stimulation of adenylate cyclase. Caffeine might decrease potassium concentrations by stimulating release of catecholamines. Calcium channel blockers enhance extrarenal disposal, due to diminished calcium-mediated potassium efflux from cells.

Hypertonicity

Hypertonicity plays an important role in maintaining the normal distribution of potassium between intracellular and extracellular compartments. In spite of hypertonicity, plasma potassium is maintained by movement of potassium out of cells, impelled by an increase in its intracellular concentration, because of contraction of intracellular volume. When the plasma glucose concentration increases, the increase in plasma osmolality induces a shift of water and potassium from the intracellular to the extracellular compartment. Normally, the efflux of potassium from cells is opposed by the action of insulin. However, in the decompensated diabetics, the combination of hyperglycemia and insuliniopenia can lead to severe hyperkalemia.

Tissue damage

Traumatic muscle injury may produce life-threatening hyperkalemia. Catabolic states result in protein breakdown to meet increased energy requirements. Skeletal muscle may release sufficient potassium to

cause severe hyperkalemia, especially in renal impairment. Accelerated breakdown of a large leukemic tumor burden, especially during induction of chemotherapy, may cause symptomatic hyperkalemia. Transient hyperkalemia occasionally occurs during hemolytic states.

Barium

Barium is an inhibitor of potassium exit channels in muscle. Hypokalemia is a feature of barium poisoning.

Summary

The distribution of potassium between intracellular and extracellular space is primarily regulated by the Na,K-ATPase pump. After dietary potassium load, insulin and catecholamine play an important role in enhancing the uptake of potassium into the cell. This can prevent a potentially serious elevation in plasma potassium concentration until the renal excretion restore potassium balance to normal. The plasma potassium concentration itself might influence potassium distribution. Potassium shifts to intracellular space in hyperkalemia and shifts to extracellular space in hypokalemia. In a variety of circumstances such as metabolic acidosis, exercise, hypertonicity, our body maintains plasma potassium concentration to constant level by redistributing potassium between the cells and the extracellular fluid.

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