Cornell University College of Veterinary Medicine

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On this Page

Physiology
Methods
Sample considerations
Test interpretation
References

Site Directory

open all | close all
About us (citation)
Copyright
Search
Donate to eClinpath

Potassium

Physiology

Potassium is the major intracellular cation (intracellular K^+ concentration is approximately 140 mEq/L) and is important for maintaining resting membrane potential of cells, particularly muscle and nerves. 60-75% of total body potassium is found within muscle cells, with the remainder in bone. Only 5% of potassium is located in extracellular fluid (ECF), therefore potassium concentration in blood is not always a reflection of total body potassium levels. Plasma (ECF) K^+ concentration is *tightly regulated*; fairly small changes can have marked effects on organ function, with severe abnormalities of plasma K^+ being life-threatening situations.

Top

eClinPath Home
Diagnostic challenge
Atlas
Calculations
Test basics
Hematology
Hemostasis
Urinalysis
Chemistry
Chemistry basics
Chemistry videos
Techniques
Sample collection
Interference indices
Quick test interpretation
Electrolytes
Fluid changes
Sodium
Potassium
Chloride
Acid Base
Minerals
Proteins
Kidney
Pancreas
Liver
Energy Metabolism
Iron Metabolism
Muscle
Ocular fluids
Cytology
Exotics

Advanced Search

Feedback

Plasma [K^+] regulation

Regulation of plasma K^+ is mostly accomplished by renal excretion and movement of K^+ from extracellular fluid to intracellular fluid (translocation). If these mechanisms are functioning normally, the amount of K^+ ingested has little effect on plasma K^+. Intake has less of an effect on plasma potassium levels, however, if one or more of the regulatory mechanisms is faulty, then the amount of K^+ ingested can exacerbate abnormalities in plasma K^+. In some species with high potassium diets (e.g. ruminants), changes in intake can affect plasma concentrations alone.

- **Intake**: Ingested K^+ is absorbed non-selectively in the stomach and small intestine. If dietary K^+ is deficient, renal excretion of K^+decreases (but still occurs) but excretion can increase under states of chronic high K^+ in the diet. Cows take in substantial amounts of potassium in their diet and, as a consequence, have high renal excretory rates of potassium (Sattler and Fecteau 2014, Schneider et al 2016).
- **Excretion**: Potassium is excreted into the renal tubules and colon, with the latter contributing only a small amount to total K^+ excretion. An additional source of potassium excretion is the saliva of ruminants (Sockett et al 1986). Control of urinary excretion of K^+ occurs in the distal tubules.
    - About 70% of filtered K^+ is absorbed in the proximal convoluted tubules of the kidney regardless of K^+ balance (via solvent drag with water and passive paracellular diffusion)
    - Around 20% is absorbed in the ascending limb of the loop of Henle (via paracellular and transcellular absorption, the latter occurring via the Na-K-2Cl transporter). Some potassium can also be excreted in this segment.
    - The remaining 10% is delivered to the distal nephron. Here, K^+ can be excreted or resorbed depending on dietary intake (deficient = absorption dominates, chronic excess = mild excretion occurs). The kidney is more efficient at excreting potassium than it is at conserving it.
        - Excretion in the distal nephron occurs mainly via renal outer medullary potassium channel or ROMK channels in principal cells in the connecting tubule, cortical collecting duct and first part of medullary collecting duct. This channel is open under basal conditions, but its activity is also linked to absorption of Na^+ by sodium transporters (ENaC), which is stimulated by aldosterone. The basolateral Na/K pumps (also stimulated by aldosterone) move potassiu from blood into the renal tubular cell for excretion. There are other K channels in the distal nephron, including maxi-K channels, which are activated by increased distal tubular flow

Top

rates (or sodium delivery, i.e. ENaC-mediated sodium absorption which creates a lumen negative potential difference, which facilitates potassium excretion), and are thought to be silent during basal states. Excretion of K^+ by the distal nephron is governed by the following, although the principle regulators are sodium absorption in the distal tubules and aldosterone:

- *Aldosterone:* Under conditions of hypochloremia or hypovolemia, the release of aldosterone stimulates sodium absorption via ENaC, which creates a negative lumen electric charge, which favors K excretion. Aldosterone increases the activity of the basolateral Na/K pump, increasing intracellular potassium concentrations, thereby promoting K^+ excretion in exchange for sodium. It also directly causes loss of potassium via increasing conductance (permeability) of the luminal membrane. Aldosterone also promotes excretion of K^+ in the colon. When aldosterone secretion is stimulated by high potassium via a direct effect on adrenal glands (versus the renin-angiotensin system when stimulated by low chloride or hypovolemia), sodium is not retained, but potassium is excreted via increased luminal membrane permeability and stimulation of the basolateral Na/K pump, which increases intracellular K concentrations.
- *Distal tubule flow rate:* Increases in flow rate (osmotic diuresis, increased urine flow after fluid therapy, diuretics, increased sodium delivery to the collecting tubules due to decreased sodium absorption higher in the nephron) enhances K^+ secretion into the tubule lumen (excretion). This works via flushing K out and enhancing distal sodium delivery, with increased absorption of sodium through ENaC (the increased lumen electronegativity caused by sodium absorption promotes potassium excretion). Decreased flow rate, such as that caused by increased proximal renal tubular resorption under conditions of hypovolemia, may lead to decreased delivery of sodium to the distal nephron, with decreased flow rates, reducing K+ excretion and thus may promote hyperkalemia.
- *Extracellular concentration of K^+*: Stimulates aldosterone release if high causing potassium excretion without sodium absorption.
- *Renal tubular lumen electronegativity*: Increased electronegativity in the collecting tubules enhances K secretion (excretion) into the tubule lumen. This can be secondary to increased sodium absorption from increased sodium delivery (see ab

for distal flow rate) or high concentrations of negatively charged molecules such as ketoacids and certain antibiotics.

- *pH:* Acidemia decreases potassium excretion (see mechanisms below under causes of hyperkalemia). Alkalemia promotes potassium loss by causing potassium to move intracellularly into the tubular cell in exchange for hydrogen. The high intracellular potassium creates a favorable concentration gradient, facilitating excretion. Alkalemia also stimulates the sodium transporter, ENaC, which increases lumen electronegativity by absorbing sodium.
- *Diet:* Dietary deficiency of K^+ will stimulate resorption (although some K^+ is always lost in the urine) whereas chronic excess will stimulate excretion (via stimulating aldosterone release and the basolateral Na/K pump).
- *ADH*: Stimulates secretion into the tubule lumen (by opening up Na/K channels in luminal membrane in principal cells of the collecting cortical duct) but also decreases excretion (by causing water absorption which decreases distal flow rates, reducing potassium excretion). So ADH likely has no effect on potassium concentrations in serum or plasma.

- Absorption in the distal nephron occurs transcellularly via α-intercalated cells, using a H-K-ATPase pump at the apical membrane) in the rest of the medullary collecting duct (other than the initial part) in exchange for H^+ (activity of these cells results in excess hydrogen secretion, which contributes to a metabolic alkalosis in states of hypokalemia).

- **Translocation**:
  - Insulin and catecholamines: Translocation of K^+ into cells from the ECF is largely dependent on insulin and catecholamines, which stimulates uptake by cells, particularly in skeletal muscle. Catecholamines stimulate the Na/K ATPase pump, which moves Na out and K in (thus decreasing serum/plasma K), in skeletal muscle. Insulin binds to a receptor on the surface of cells (insulin substrate receptor-1). Downstream signaling with this receptor causes uptake of K and glucose (the latter via GLUT-4 receptors).
  - Tissue necrosis can also cause release of intracellular potassium, particularly in skeletal muscle.
  - Alterations in acid-base status: Shifts of K^+ in and out of cells can also occur with changes in the pH of ECF. Specifically, alkalosis (when the dominating disturbance or in alkalemic states) causes potassium to move into cells resulting in hypokalemia. A mineral metabolic acidosis (hyperchloremic) can directly cause a transient hyperkalemia by stimulating potassium movement

Top

out of cells or decreased potassium uptake by cells. This is mediated by the drop in extracellular pH, which inhibits Na/H exchange (H out, Na into the cell) and drops intracellular sodium concentrations. Decreased intracellular sodium *decreases* the activity of the Na/K pump (which moves 3Na out for 2K in), which is dependent on **intracellular** sodium concentrations. In contrast, accumulation of a non-chloride containing acid in a titration or high anion gap acidosis does not directly cause a hyperkalemia through translocation. This is because the organic acid (e.g. L-lactate) and the H it is carrying move together into the cell (via monocarboxylate transporters, e.g. MCT1) and the drop in **intra**cellular pH is more severe than with a mineral acidosis. The lower **intra**cellular pH drives Na/bicarbonate or Na/H exchange (Na in, bicarbonate or H out), so the intracellular Na concentrations remains high and stimulates Na/K activity (drives Na out and K in), such that K does not increase in blood with a high anion gap acidosis. The hyperkalemia that is frequently seen in animals with a titration acidosis, is thought to be secondary to decreased renal excretion and **not** translocation (see mechanisms below) (effect of pH on renal handling of potassium is reviewed by Hamm et al 2013). In fact, under experimental conditions, organic acidoses are associated with normal or low potassium (Aronson and Giebisch 2011). With alterations in acid-base status, changes in potassium (decrease in alkalosis and increase in a mineral acidosis) are more severe with primary metabolic than primary respiratory conditions.

- Endotoxins: This stimulates the Na/K pump and causes insulin release, both of which will drive K inside cells.

Methods

Serum or plasma concentrations of these major electrolytes can be measured by ion-specific electrodes or flame photometry. Measurement of electrolytes by ion-specific electrodes is called potentiometry. There are two types of potentiometry: direct and indirect. Direct potentiometry is utilized by blood gas machines and does not involve sample dilution. Indirect potentiometry is utilized by automated chemistry analyzers, such as the ones used at Cornell University, and involves sample dilution before analysis. This distinction is important because endogenous interferents such as lipemia may falsely decrease electrolyte concentrations with indirect, but not direct, potentiometry.

Technique used at Cornell

Feedback Top

Direct (blood gas machine) or indirect (chemistry analyzer) potentiometry. On our chemistry profiles, indirect potentiometry is used to obtain potassium results.

Procedure

With this technique, an electrode containing an internal electrolyte solution is immersed in the patient sample, which is separated from the internal solution by a membrane that can detect the electromotive force (EMF) generated by the ions in both solution. This EMF is determined by the difference in concentration of the test ion in the test solution and internal filling solution (test ion at fixed concentration). The EMF is predicted by the Nernst equation (see techniques for more details on the method). For testing purposes with the chemistry analyzer, the sample is diluted 1:32 before analysis (indirect potentiometry).

Units of measurement

The concentration of potassium is measured in mEq/L (conventional units, used at Cornell), mg/dL (conventional units), or mmol/L (SI units). The conversion formula is shown below:

$$mEq/L \times 1 = mmol/L$$
$$mg/dL \div 3.9 = mmol/L$$

Sample considerations

Sample type

Serum, plasma, and urine. Plasma provides more accurate values than serum because potassium is released from platelets during clotting.

Anticoagulant

Heparin is the preferred anticoagulant. K_3EDTA should be avoided because it will cause spuriously high levels of K^+ in sample due to potassium in the anticoagulant.

- **Bovine**: Internal studies in the Clinical Pathology Laboratory at Cornell University in bovine blood show that values in heparinized plasma are slightly higher (0-0.3 mEq/L) than in serum (Naeves and Stokol, unpublished data).

Top

Stability

- **Human**: Per reagent manufacturer product information sheet
  - *Serum and plasma*: 2 weeks at room temperature, 2 weeks refrigerated.
  - *Urine*: Store at 4°C
- **Bovine**: Internal studies in the Clinical Pathology Laboratory at Cornell University show that potassium is more stable in heparinized whole blood versus unseparated clotted whole blood and is more stable at 22°C than 4°C. The increased stability at 4°C is attributed to increased inhibition of the Na/K ATPase in cells (which drives K in and sodium out), resulting in higher extracellular potassium.
  - *Heparin/green top tubes*: Potassium results are more stable in heparinized whole blood samples (not separated) maintained at 22°C (no change in results at 4 or 6 hours after collection) compared to 4°C (increased by 0.1-0.2 mEq/L by 4 hours and by 0.2-0.3 mEq/L at 6 hours) after collection.
  - *Clot tubes*: Potassium values are mildly increased in whole blood maintained at 4°C (by 0.1-0.3 mEq/L) or 22°C (by 0.1-0.2 mEq/L) for 4 hours (Naeves and Stokol, unpublished data).

Regardless of the above findings in cattle, which only pertain to storage for up to 4-6 hours, it is still recommended that serum or plasma should be removed *immediately* from cells after collection (by centrifugation), to avoid falsely increased K^+ levels, caused by release of K^+ from intracellular stores in cells (potassium is much higher in cells than in ECF). Red blood cells and platelets are the major sources of intracellular potassium, however only certain species (horses, some breeds of cattle such as Holstein, pigs, llamas) have high potassium in red blood cells. Dogs do not have high potassium in red blood cells, except for certain breeds of dogs (Japanese or other Asian breeds, e.g. Akita, Shiba Inu). Also, reticulocytes in all dog breeds are rich in potassium. Leakage of potassium from cells can occur without overt hemolysis and will also occur in serum separator tubes if serum is not separated from the red blood cells. A falsely high potassium is one of the most common artifacts seen on chemistry panels from samples that are mailed Cornell laboratory from horses, camelids and cattle (since we see blood from Holsteins, primarily), when the serum or plasma has not been separated from cells.

Interferences

- **Lipemia**: Marked lipemia (triglycerides >600 mg/dL) may mildly decrease potassium due to the solvent exclusion effect. This is based on internal observations comparing the results of direct and indirect

Top

potentiometry on the same sample from markedly hypertriglyceridemic dogs. The effect on potassium is small (e.g. 0.3-0.5 mEq/L decrease) compared to that of sodium and chloride.

- **Hemolysis**: Hemolysis or altered red blood cell membrane stability without hemolysis (e.g. with storage) may increase serum or plasma potassium in species or breeds with high potassium red blood cells (horses, camelids, pigs, some breeds of cattle such as Holstein, some Asian dog breeds) or in dogs with a marked reticulocytosis.
- **Icterus**: No effect.

Test interpretation

Hyperkalemia

Hyperkalemia increases the resting membrane potential (i.e. makes it less negative so that it is easier to polarize or become activated, e.g. increase from -90 to -80). This predisposes the cell to being over-excitable and results in muscle and nerve excitability, the most serious consequence of which is cardiac arrythmias and even arrest (remember, high KCl can be used as a euthanasia solution to induce cardiac arrest). Hyperkalemia can potentially contribute somewhat to an acidosis by inhibiting renal ammoniagenesis (the main way the kidney eliminates acids) (Hamm et al 2013).

- **Artifact:**
  - *Serum:* Serum K^+ is generally higher than plasma K^+ due to release of K^+ from platelets during clotting. Based on internal studies at Cornell (such as when we established our reference intervals on serum and plasma from related species) and previous reports, the difference between serum and plasma K^+ in animals with normal platelet counts can be as high as 0.7 mEq/L in dogs, 1.6 mEq/L in cats, 1.6 mEq/L in horses, 0.5 mEq/L in Holstein cattle (this may be due to hemolysis in the samples) and 0.8 mEq/L in alpacas. This difference could be higher (but not hugely) in animals with thrombocytosis (particularly if the latter is marked, i.e. > 1 million/uL). Thus, heparinized plasma is the preferred sample for potassium measurement.
  - *Hemolysis (in vivo or in vitro) or leakage from RBCs:* Intravascular (*in vivo*) hemolysis in a hemolytic anemia, artifactual (*in vitro*) hemolysis or leakage from RBCs with storage or poor sample handling, may increase K^+ in animals with high K^+ in their erythrocytes, including horses, pigs (Di Martino e al 2015), some cattle breeds (e.g. Holstein), caribou (internal studies at Cornell) and camelids. T will depend on the degree of hemolysis or RBC membrane disruption (more likely if high). A high

potassium is one of the most common falsely abnormal chemistry results (along with falsely low glucose) in mailed in samples, in which serum or plasma has not been separated from cells in these aforementioned species. Certain dog breeds also have high K+ in their mature red blood cells, such as Akitas and other Japanese breeds. All dogs have high K^+ in their *reticulocytes*, so K^+ can be falsely increased in hemolyzed samples (or samples with delayed separation from cells) with very high reticulocyte counts from any dog breed.

- *Leukocytosis:* Very high leukocyte counts (> 100,000/uL) can potentially result in hyperkalemia due to leakage of intracellular K^+ from cells. We have not really identified such cases.
- *K^+ EDTA anticoagulant:* Contamination of serum/plasma sample with K^+ EDTA will result in very high (non-physiologic) K^+ values (>20 mEq/L) as well as marked hypocalcemia (<5 mg/dL; due to chelation). We see this unavoidable artifact occasionally in samples.
- *Contamination with high potassium fluids:* If a blood sample is taken from an unflushed intravenous line used to administer potassium-rich fluids, K^+ could be falsely high.

- **Physiologic:**
  - *Age*: Potassium is reported to be higher in foals < 5 months of age than adult horses. Foals < 1 week old are reported to have higher K^+ than foals > 1 week old.
- **Iatrogenic:** Supplementation of potassium in intravenous fluids does not usually result in hyperkalemia if kidney function is normal.
- **Pathophysiologic:**
  - *Transcellular shifts:* Shifting of K^+ from intracellular fluid (ICF) to ECF occurs with substantial tissue necrosis, exercise (this occurs especially in horses and is due to release of K^+ from muscles, particularly skeletal muscles which are of high mass; K^+ is a local vasodilator for muscle cells), uroperitoneum (in foals and small animals – shifts from abdomen where urine is high in K^+ into blood), hypertonicity (e.g. diabetes mellitus; occurs due to solvent drag), insulin deficiency (e.g. diabetes mellitus) and potentially a hyperchloremic metabolic acidosis (a transient hyperkalemia is seen after experimental infusion of ammonium chloride in dogs). A high anion gap or titration metabolic acidosis (accumulation of a non-chloride acid, e.g. lactate, uremic phosphate-based acids) does not usually result in hyperkalemia. Hyperkalemia in animals with a titration acidosis is usually not due to translocation, but is thought to be due to decreased renal excretion of K^+ (see below).

Feedback

Top

- *Hyperkalemic polymyopathy of horses:* This is due to a genetic defect in the alpha subunit of the sodium channel of muscle cells (the sodium channels remain perpetually open) observed in Quarterhorses and other heavily muscled breeds like Appaloosas and Paints. It is a familial condition in the Quarterhorse and appears to be inherited as an autosomal dominant condition. The condition appears to be clinically worse in males. It is characterized by intermittent episodes of muscle fasciculation and weakness concurrent with increases in serum K^+ values, which is likely due to leakage from muscle due to the defective channels. Normokalemic variants have been described. In Quarterhorses, a single point mutation in the ryanodine receptor, an intracellular calcium channel, causes excessive calcium inside muscles, resulting in a myopathy with subsequent release of potassium (Alerman et al 2009).

- *Decreased renal excretion*: Hyperkalemia is a feature of *anuric* or *oliguric* acute renal failure, urinary tract obstruction or rupture (as indicated above), and hypoaldosteronism (Addison's disease).

  - *Neonatal bovine diarrhea:* Calf scours is associated with hyperkalemia. In two studies of 124 and 836 calves with diarrhea, 28-34% had hyperkalemia with fewer having hypokalemia (11% on one of the studies) (Trefz et al 20133a, Treftz et al 2013b). In both studies, the hyperkalemia was associated with severity of dehydration, as shown by azotemia, hyperphosphatemia and L-lactic acidosis. The azotemia may all be prerenal from hypovolemia or a combination of prerenal and secondary renal azotemia. The hyperphosphatemia was attributed to the azotemia, and acidemia causing breakdown of intracellular organic phosphate (which presumably turns into inorganic phosphate). The hyperkalemia in these calves was attributed to decreased renal excretion principally from hypovolemia (due to the association with azotemia, and L-lactic acidosis), with a possible contribution by acidemia. Hypovolemia would promote proximal renal resorption of sodium, decreasing distal delivery and distal flow rates, resulting in potassium retention (since excretion is dependent on flow rates, with higher flow rates leading to more excretion). The acidemia would also promote distal potassium excretion, via mechanisms indicated below. Hyperkalemia was not associated with a D-lactic acidosis (e.g. ruminal drinking), which does cause acidemia but is not associated with hypovolemia. The lack of association between hyperkalemia and D-lactic acidosis was postulated to be secondary to the lack of dehydration in the latter syndrome, combined with obligate potassium losses with D-lactat which is eliminated by the kidney (Trefz et al 2013a). Even though aldosterone levels are

Top

positively correlated with potassium concentrations in these calves (Trefz and Lorenz 2017), other renal responses (presumably from the hypovolemia and L-lactate acidosis) are likely dominating. It is also possible that these hypovolemic calves with diarrhea, including those with prerenal azotemia, have decreased salivary excretion of potassium, contributing to the hyperkalemia.

- *Uroabdomen*: Dogs, cats and horses with uroabdomen frequently have high potassium due to decreased renal excretion. Although some cattle with uroabdomen can have hyperkalemia (Smith et al 1983, Hylton and Trent 1987), experimental urinary tract obstruction did not lead to hyperkalemia, which was attributed to increased excretion of potassium in saliva (Sockett et al 1986).
- *Addison's disease (hypoaldesteronism)* causes a low sodium and high potassium with a sodium:potassium ratio of < 27:1. Electrolyte changes (high K^+, low Na^+) mimicking Addison's disease can be seen with repeated drainage of thoracic effusions, severe diarrhea (e.g. Salmonella or whipworm infection), and lymphangiosarcoma, although the precise mechanism is unclear. Measurement of the sodium to potassium ratio is **not** a sensitive or specific diagnostic test for Addison's disease (it will be normal in variants of Addison's disease, in which mineralocorticoids are normal but glucocorticoids are deficient). This is most common in the dog and rare in other species. It is reported that horses in chronic renal failure can have high potassium, which is attributed to secondary hypoaldosteronism.
- *Acidosis (particularly when the dominating disturbance)*: Acidosis (metabolic or respiratory) decreases K+ excretion and promotes resorption in the distal nephron. Decreased excretion is due to decreased activity of the basolateral Na/K pump (that drives potassium excretion into the urine by principal cells in the distal nephron) and higher resistance (decreased conductance) of the apical membrane of principal cells. Decreased excretion is also thought to be secondary to increased renal ammoniagenesis – ammonia inhibits sodium absorption by the sodium epithelial channel in the distal and collecting tubules (which is linked to potassium excretion by principal cells) and may affect the luminal K channels, which excrete potassium in the urine. Potassium absorption by intercalated cells is also stimulated via acidosis activating the H/K pump (causing distal tubular excretion of hydrogen, an appropriate corrective response to a metabolic acidosis and a compensatory response to respiratory acidosis) in exchange for absorption of potassium. However, remember that potassium excretion will often be increased in disease states associated with a metabolic

Feedback

Top

acidosis, in particular. For instance, with hypovolemia stimulating lactic acidosis, even though the acidosis may be promoting potassium absorption/decreased excretion (which will increase potassium in blood), aldosterone and ADH will be stimulating sodium and water resorption, with aldosterone causing potassium excretion. So the potassium concentration in blood will reflect the opposing effects of aldosterone (stimulating K excretion) and acidosis (promoting K retention). In neonatal calves with diarrhea, L-lactate acidosis and hyperkalemia, lactate appears to stimulate potassium retention despite high concentrations of aldosterone (Trefz and Lorenz 2017). In states of chronic acidosis, proximal tubular sodium (and water) absorption is inhibited leading to increased distal sodium delivery, distal flow rates and potassium excretion, which would favor hypokalemia in blood (Hamm et al 2013).

- *Other mechanisms*
  - *Decreased salivary excretion*: Marked dehydration in ruminants could cause a hyperkalemia due to decreased saliva production, particularly if there is concurrent renal dysfunction. This is uncommon, since anorexic cattle often have low potassium, which offsets any increases from decreased saliva production.

Hypokalemia

Hypokalemia decreases the resting membrane potential of cells (i.e. makes it more negative, which hyperpolarizes the cells, making them less sensitive to stimuli, e.g. -90 to -95). This means that muscles and nerves are weaker and require larger stimuli to be activated resulting in muscle weakness and arrythmias. Hypokalemia also interferes with ADH action on renal tubules and alters blood flow through the vasa recta, depleting the medullary interstitium of solutes, contributing to defective concentrating ability. Hypokalemia also contributes to (or worsens) or causes a metabolic alkalosis (in states of chronic hypokalemia, which is rare in veterinary medicine) by stimulating hydrogen excretion in the proximal and distal tubules. In the proximal tubule, the luminal Na/H pump and basolateral Na/bicarbonate transporter are stimulated, resulting in net resorption of sodium and bicarbonate, in exchange for hydrogen loss. In the distal tubule, both the luminal H/K pump and H-ATPase pump are stimulated resulting in hydrogen excretion in exchange for potassium absorption. In a pre-existing metabolic alkalosis (e.g. displaced abomasa in ruminants), depletion of potassium can exacerbate the alkalosis via stimulating renal hydrogen excretion in proximal and distal tubules (which is worsened by sodium avidity in the kidney, which promotes sodium resorption with bicarbonate) (Hamm et al 2013). Hypokalemia is

usually due to gastrointestinal or renal losses of potassium. Remember that blood K^+ values are not always a reflection of total body K^+ stores; K^+ values can be normal in blood, despite severe deficits in total body K^+.

- **Artifact:** Severe lipemia and possibly hyperglobulinemia (due to immunoglobulins) may result in a mild hypokalemia (pseudohypokalemia) due to solvent exclusion/volume displacement when potassium is measured using diluted plasma (indirect potentiometry; the technique routinely used for electrolyte measurement). This artifact can be overcome by using undiluted plasma (direct potentiometry) for measuring potassium (i.e. a blood-gas analyzer). The changes in potassium with solvent exclusion are far less than those seen with sodium and chloride.
- **Pathophysiologic:**
    - *Decreased intake:* This occurs with anorexia (not just inappetence or decreased appetite) in large animals, including horses (especially foals), camelids and cows (due to their high dietary intake and high urinary excretion of potassium). The kidney cannot decrease excretion of potassium quickly enough to prevent a rapid drop in potassium that occurs with anorexia in these species. Decreased intake in small animals rarely results in hypokalemia unless there are additional losses of potassium. Hypokalemia can be seen in cats fed low potassium diets.
    - *Transcellular shifts:* Shifting of K^+ from ECF to ICF occurs with primary respiratory or primary metabolic alkalosis resulting in *alkalemia* (where hydrogen moves extracellularly in exchange for potassium), insulin release (usually spikes of insulin such as that seen after glucose infusion or eating) or administration, and catecholamine release (from epinephrine stimulating β2-adrenergic receptors and activating the sodium-potassium [Na/K] ATPase pump in muscle). Similarly, endotoxemia may also result in hypokalemia because endotoxins also stimulate the Na/K ATPase pump in muscle cells and promote insulin release. Transcellular shifting due to alkalemia usually produces small changes in potassium (unless there are concurrent losses of potassium). The hypokalemia that occurs with respiratory alkalosis is usually transient and not seen in human patients with a chronic respiratory alkalosis.
    - *Increased loss:* The potassium deficit will be enhanced if intake of potassium is decreased.
        - *Gastrointestinal losses:* Causes include vomiting of gastric contents (the loss of chloride enhances K^+ excretion in the kidneys, promoting the hypokalemia), abomasal stasis (e.g. vagal digestion or atony), outflow obstruction or torsion, and diarrhea. Diarrhea in horses a cattle often produces a hypokalemia. Severe diarrhea and vomiting in dogs and cats can

also result in hypokalemia. Saliva is potassium-rich and disorders such as choke in horses and cattle can result in hypokalemia.

- *Third space losses/sequestration:* Accumulation of fluid in body cavities (e.g. peritonitis) or distended gastrointestinal system (e.g. volvulus, ileus) can result in hypokalemia. This may be dilutional from perceived volume depletion due to losses of fluid from the intravascular space, which results in secretion of ADH (retains water in kidney) and stimulation of thirst.
- *Cutaneous losses:* Sweating (horses).
- *Renal losses:* Renal losses of potassium can occur via several mechanisms, the main one being aldosterone, which stimulates sodium absorption in exchange for potassium excretion in the principal cells of the late distal tubule and collecting tubules.
    - *Aldosterone* is stimulated by the renin-angiotensin system in response to hypovolemia and decreased delivery of chloride (hypochloremia) to the macula densa. Hyperaldosteronism is a rare condition causing severe hypokalemia in dogs and cats and is usually secondary to adrenal neoplasia (in dogs) or hyperplasia (cats).
    - *Increased distal tubular flow rate:* Potassium excretion is also enhanced by increased distal tubule flow rates, i.e. any cause of polyuria (e.g. osmotic diuresis with glucosuria, post-obstructive diuresis)
    - *Increased lumen electronegativity*, e.g. high concentrations of unadsorbable anions in the renal tubule lumen, e.g. penicillin, ketones, decrease the positive charge within the lumen, which causes the positively charged potassium to get excreted.
    - *Primary metabolic alkalosis (particularly if the dominating acid-base disturbance with mixed disturbances or in states of alkalemia):* Hydrogen is released from internal cellular buffers (e.g. hemoglobin) into blood to buffer the accumulated bicarbonate. To maintain electroneutrality, potassium moves into cells. In the renal tubules, this will create a concentration gradient between the cell and the renal tubular lumen that will promote potassium excretion into the lumen. In addition, alkalosis increases the activity of the potassium channels in principal cells (promoting excretion). Excretion will also be promoted by increased bicarbonate in the urine (increasing lumen electronegativity) and low urine chloride (frequently seen with metabolic alkalosis – the low chloride stimulates activity of the luminal KCl channel in the principal cell) (Hamm et al 2013).

Feedback

Top

- *Renal tubular disease:* Potassium wasting also occurs if there is renal tubule disease that prevents the normal absorption of filtered potassium, e.g. proximal renal tubular acidosis, chronic renal disease in cats.
- *Loop diuretics*: These inhibit the NaK2Cl pump in the thick ascending limb of the loop of Henle. The lack of K^+ absorption is exacerbated by a luminal K channel, which secretes K^+ actively into the urine (which is normally required for correct operation of the NaK2Cl pump).

- *Syndrome of hypokalemia in cattle*: Dairy cattle in the first 3 months after calving appear to be predisposed to a hypokalemic syndrome, which manifests as weakness, recumbency, decreased muscle tone and depression. The main cause appears to be administration of isofluprednone acetate, which has mineralocorticoid effects, but anorexia and dextrose or insulin administration can compound the hypokalemia. Low potassium concentrations are found on testing (<2.2-2.5 mEq/L) but may be higher if there is concurrent muscle necrosis (releasing intramuscular stores of potassium) in downer cows. Because there is concurrent muscle weakness in the gastrointestinal tract and rumen stasis, affected animals also frequently have a primary hypochloremic metabolic alkalosis. They can be concurrently hypophosphatemic (mechanism unclear). Affected cattle still have high urinary excretion of potassium, which is not surprising with administration of isofluprednone acetate but with other circumstances, e.g. anorexia, could be the acute onset of the condition, with continued high urinary excretion of potassium (Sattler and Fecteau 2014).

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Top

Top