Research Article

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Role of Gibbs-Donnan Equilibrium and Transmembrane Electrochemical Gradient in Defining the Plasma Potassium Concentration

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ABSTRACT

Potassium is the most abundant exchangeable cation in the body. Most potassium resides in the intracellular compartment (ICF), and a small amount is in the interstitial fluid compartment (ISF) and plasma space. Both plasma and intracellular potassium ions are in equilibrium with potassium ions in the interstitial fluid compartment (ISF). The distribution of potassium between the plasma and ISF is determined by the electrochemical gradient imposed by the presence of negatively charged, impermeant albumin molecules and is known as Gibbs-Donnan equilibrium. The potassium ions in the ISF are in turn in equilibrium with intracellular potassium ions as defined by the transmembrane electrochemical gradient. Current analysis relating the plasma potassium concentration $[K^+]_p$ with the intracellular potassium concentration $[K^+]_{ICF}$ implicitly assumes that the plasma water potassium concentration $[K^+]_{pw}$ is equal to the interstitial fluid potassium concentration $[K^+]_{ISF}$.This is inaccurate since the $[K^+]_{pw}$ is greater than $[K^+]_{ISF}$ due to Gibbs-Donnan equilibrium. Given that hypokalemia and hyperkalemia are disorders of potassium balance that reflect changes in the intracellular potassium store, a new equation is derived to define the quantitative interrelationship between the $[K^+]_p$ and $[K^+]_{ICF}$ taking into account the three compartmental distribution of potassium in the body fluids.

INTRODUCTION

Potassium is present in all body tissues, and it is necessary for normal cellular function due to its role in maintaining intracellular fluid volume and transmembrane electrochemical gradient. Although disorders of potassium balance are clinically based on changes in the plasma potassium concentration $[K^+]_p$, it is well known that changes in the total body potassium stores predominantly originate from the intracellular compartment (ICF). Indeed, the plasma potassium concentration, $[K^+]_p$, ranges from 3.5 to 5 meq/L, whereas the intracellular potassium concentration $[K^+]_{ICF}$ ranges from 140 to 150 meq/L [1]. Currently, there is no formula that defines the quantitative interrelationship between the $[K^+]_p$ and $[K^+]_{ICF}$. In this article, a new equation is derived to quantify the interrelationship between $[K^+]_p$ and $[K^+]_{ICF}$ based on the three compartmental distribution of potassium resulting from Gibbs-Donnan equilibrium and transmembrane electrochemical gradient.

A New Formula Defining the Quantitative Interrelationship Between the $[K^+]_p$ and $[K^+]_{ICF}$

The distribution of potassium ions between the plasma and interstitial fluid (ISF) is defined by Gibbs-Donnan Equilibrium (2): Figure 1

$$FE_G + RT\ln([K^+]_{pw}/[K^+]_{ISF}) = 0 \quad \text{(Eq.1)}$$

where F = Faraday's constant

E_G = electrical potential imposed by negatively charged, impermeant plasma proteins

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R = ideal gas constant

T = absolute temperature in Kelvin

$[K^+]_{pw}$= plasma water potassium concentration

$[K^+]_{ISF}$= interstitial fluid potassium concentration

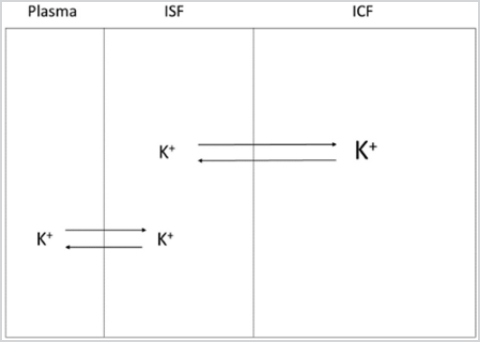

Figure 1: Three-Compartmental Distribution of Potassium- The distribution of potassium between the plasma and interstitial fluid compartments is defined by Gibbs-Donnan equilibrium, whereas the distribution of potassium between the interstitial fluid and intracellular fluid compartments is defined by the transmembrane electrochemical gradient. Although disorders of potassium balance are clinically diagnosed by changes in the plasma potassium concentration, it is well appreciated that changes in the plasma potassium concentration reflect alterations in the total body potassium store that originate predominantly from the intracellular potassium compartment. Therefore, changes in the plasma potassium concentration are simply a reflection of changes in the intracellular potassium concentration.

$$\ln([K^+]_{pw}/[K^+]_{ISF}) = -FE_G/RT \qquad \text{(Eq.1A)}$$

$$[K^+]_{pw} = [K^+]_{ISF}\,(e^{-FE_G/RT}) \qquad \text{(Eq.1B)}$$

The transmembrane electrical gradient is defined by the Goldman-Hodgkin-Katz equation (3,4):

$$V_m = RT/F\ ln((P_{K^+}[K^+]_{ISF}+P_{Na^+}[Na^+]_{ISF}+P_{Cl^-}[Cl^-]_{ICF})/(P_{K^+}[K^+]_{ICF}+P_{Na^+}[Na^+]_{ICF}+P_{Cl^-}[Cl^-]_{ISF})) \qquad \text{(Eq.2)}$$

where V_m = potential difference across the cell membrane

F = Faraday's constant

R = ideal gas constant

T = absolute temperature in Kelvin

P_{K^+} = permeability of the membrane to potassium

P_{Na^+} = permeability of the membrane to sodium

P_{Cl^-}= permeability of the membrane to chloride

$[K^+]_{ICF}$ = intracellular fluid potassium concentration

$[K^+]_{ISF}$= interstitial fluid potassium concentration

$[Na^+]_{ICF}$= intracellular fluid sodium concentration

$[Na^+]_{ISF}$= interstitial fluid sodium concentration

$[Cl^-]_{ICF}$= intracellular fluid chloride concentration

$[Cl^-]_{ISF}$= interstitial fluid chloride concentration

$$FV_m/RT = \ln((P_{K^+}[K^+]_{ISF}+P_{Na^+}[Na^+]_{ISF}+P_{Cl^-}[Cl^-]_{ICF})/(P_{K^+}[K^+]_{ICF}+P_{Na^+}[Na^+]_{ICF}+P_{Cl^-}[Cl^-]_{ISF})) \qquad \text{(Eq. 2A)}$$

$$e^{FVm/RT} = ((P_{K^+}[K^+]_{ISF}+P_{Na^+}[Na^+]_{ISF}+P_{Cl^-}[Cl^-]_{ICF})/(P_{K^+}[K^+]_{ICF}+P_{Na^+}[Na^+]_{ICF}+P_{Cl^-}[Cl^-]_{ISF})) \qquad \text{(Eq. 2B)}$$

$$[K^+]_{ISF} = ([e^{FVm/RT}(P_{K^+}[K^+]_{ICF}+P_{Na^+}[Na^+]_{ICF}+P_{Cl^-}[Cl^-]_{ISF})-P_{Na^+}[Na^+]_{ISF}-P_{Cl^-}[Cl^-]_{ICF}]/P_{K+}) \qquad \text{(Eq.2C)}$$

Incorporating Eq. 2C into Eq. 1B:

$$\therefore [K^+]_{pw} = ([e^{FVm/RT}(P_{K^+}[K^+]_{ICF}+P_{Na^+}[Na^+]_{ICF}+P_{Cl^-}[Cl^-]_{ISF})-P_{Na^+}[Na^+]_{ISF}-P_{Cl^-}[Cl^-]_{ICF}]/P_{K+})\ (e^{-FE_G/RT}) \qquad \text{(Eq.3)}$$

Since the plasma water potassium concentration $[K^+]_{pw}$ is related to the plasma potassium concentration $[K^+]_p$ by the mass concentration of water, (pH_2O) (5):

$$[K^+]_{pw}\,(pH_2O)=[K^+]_p \quad \text{(Eq.4)}$$

$$\therefore [K^+]_p=([e^{FVm/RT}(P_{K^+}[K^+]_{ICF}+P_{Na^+}[Na^+]_{ICF}+P_{Cl^-}[Cl^-]_{ISF})-P_{Na^+}[Na^+]_{ISF}-P_{Cl^-}[Cl^-]_{ICF}]/\,P_{K+})\,(e^{-FE_d/RT})\,(pH_2O) \quad \text{(Eq.5)}$$

DISCUSSION

Although disorders of potassium balance are clinically diagnosed by changes in the plasma potassium concentration, it is well appreciated that changes in the plasma potassium concentration reflect alterations in the total body potassium content that originate predominantly from the intracellular potassium compartment [1]. Currently, the quantitative interrelationship between the plasma potassium concentration and intracellular potassium concentration is not known. In this article, a new mathematical equation is derived to quantify the interrelationship between the plasma potassium concentration and intracellular potassium concentration since changes in the plasma potassium concentration ultimately reflects alterations in the intracellular potassium concentration.

It is well known that the plasma water potassium concentration $[K^+]_{pw}$ is greater than the interstitial fluid potassium concentration $[K^+]_{ISF}$ due to Gibbs-Donnan equilibrium (6,7). The presence of negatively charged, impermeant plasma proteins will tend to attract potassium ions from the interstitial fluid into the plasma space, thereby resulting in a higher $[K^+]_{pw}$. At Gibbs-Donnan equilibrium, the freely diffusible potassium ions will distribute in such a manner that its chemical gradient is equal in magnitude to the electrical gradient imposed by the negatively charged, impermeant plasma proteins as defined by Eq. 1. As a result, the potassium concentration in the interstitial fluid is typically 0.95 times the potassium concentration in the plasma [6]. Potassium ions in the interstitial fluid are in turn in equilibrium with intracellular potassium ions as defined by the transmembrane electrochemical gradient [8]. Potassium is present at higher concentration inside the cell than outside, whereas sodium and chloride are present at higher concentration outside the cell [8]. Due to its concentration gradient, potassium will diffuse across the cell membrane from the intracellular compartment to the interstitial fluid compartment. As potassium leaves the cell, an excess of positive charge builds up on the exterior of the cell membrane, and an excess of negative charge builds up on the interior of the cell. Consequently, the interior of the cell becomes negative relative to the exterior, generating a difference in electrical potential across the membrane. Since like charges repel and unlike charges attract each other, the electronegative cell interior and electropositive cell exterior will in turn oppose the diffusive movement of potassium down its concentration gradient. When the electrical potential difference across the cell membrane is equal to the chemical force driving potassium out of the cell, there is no net movement of potassium in either direction and electrochemical equilibrium is attained. The electrical potential difference across the cell membrane that exactly opposes the chemical gradient for an ion is known as the equilibrium potential. The magnitude of this equilibrium potential is therefore a function of the concentration gradient for the ion. For a cell where there is only one permeant ion, the equilibrium potential for that ion will be equal to the resting membrane potential of the cell. However, the resting membrane potential is slightly less negative than the potassium equilibrium potential because other types of ions also contribute to the resting membrane potential. In addition to potassium, the cells are also permeable to sodium and chloride. In particular, permeability to sodium is the main reason for the difference in the resting membrane potential from the potassium equilibrium potential. Since the sodium concentration is much higher outside of a cell than inside, sodium will diffuse down its chemical gradient into the cell, making the cell interior more positive relative to the outside. Therefore, the sodium equilibrium potential that exactly opposes the sodium concentration gradient will be positive. If sodium were to be the only permeant ion, the resting membrane potential will be positive. Since both sodium and potassium are able to cross the membrane, the resting membrane potential will be in between the sodium equilibrium potential and potassium equilibrium potential. Given that the resting membrane is much more permeable to potassium than to sodium, the resting membrane potential is closer to the potassium equilibrium potential than to the sodium equilibrium potential.

Therefore, the transmembrane sodium and potassium concentration gradients are key determinants of the membrane potential and are maintained by the activity of the Na^+-K^+ ATPase, which actively transports sodium and potassium against their electrochemical gradients.

Similarly, the chloride concentration gradient also contributes to the resting membrane potential. Consequently, in determining the resting membrane potential across the cell membrane in which Na^+,K^+ and Cl^- are the major contributors to the membrane potential, the Goldman-Hodgkin-Katz equation was derived to account for the selectivity of the membrane's permeability to sodium, potassium and chloride ions [3,4]. Currently, it is implicitly assumed that the interrelationship between the plasma potassium concentration $[K^+]_p$ and intracellular potassium concentration $[K^+]_{ICF}$ is defined by the Goldman-Hodgkin-Katz equation by inaccurately assuming that the plasma water potassium concentration is equal to the interstitial fluid potassium concentration $[K^+]_{ISF}$. However, due to Gibbs-Donnan equilibrium, the potassium concentration in the interstitial fluid is typically 0.95 times the potassium concentration in the plasma [6].

Given that hypokalemia and hyperkalemia are disorders of potassium balance which predominantly reflect changes in the intracellular potassium store, a new formula, Eq. 5, is derived to define the quantitative interrelationship between the plasma potassium concentration $[K^+]_p$ and intracellular potassium concentration $[K^+]_{ICF}$. Eq. 5 is derived based on the three compartmental distribution of potassium among the plasma, interstitial fluid and intracellular fluid compartments as defined by Gibbs-Donnan equilibrium (Eq. 1) and transmembrane electrochemical gradient (as defined as the Goldman-Hodgkin-Katz equation, Eq.2). Eq. 5 also incorporates the mass concentration of water in its derivation to account for the fact that the plasma is normally composed of 93% plasma water and that the plasma potassium concentration is 0.93 times the plasma water potassium concentration: $[K^+]_{pw}\,(0.93) = [K^+]_p$ (9).

CLINICAL IMPLICATIONS

It is well known that changes in the serum sodium concentration are sensed by osmoreceptors in the hypothalamus,

whereas changes in the serum calcium level are sensed by calcium-sensing receptors in the parathyroid cell, kidneys and other tissues [10,11]. How are changes in the serum potassium concentration sensed by the cells? Changes in potassium balance will initially result in changes in the serum potassium concentration. Changes in the serum potassium concentration will in turn lead to a subsequent change in interstitial fluid potassium concentration due to reestablishment of Gibbs-Donnan equilibrium. The change in interstitial fluid potassium concentration will then alter the transmembrane electrochemical gradient, resulting in the transcellular shift of potassium across the cells and a subsequent change in the resting membrane potential. Therefore, fluctuations in the serum potassium concentration are sensed by the cells by an alteration in the membrane potential. Indeed, the cell membrane hyperpolarizes or depolarizes in response to a decrease or increase in serum potassium concentration respectively [12]. It is also known that hyperpolarization or depolarization of the cell membrane disrupts normal electrical excitability and can potentially lead to life-threatening cardiac arrhythmias (12). Alterations in the serum potassium concentration are therefore sensed by the cells via changes in the $[K^+]_{ICF}$ (intracellular fluid potassium concentration) and V_m (membrane potential) as reflected by these terms in Eq. 5.

Based on Eq. 5, hyperpolarization of the cell membrane induced by hypokalemia will in turn lead to re-establishment of the electrochemical gradient for sodium, resulting in increased transcellular sodium entry. Indeed, a deficit of intracellular potassium may result in the entry of sodium ions into the cell as supported by the finding of an increase in non extracellular sodium and an increased ratio of non extracellular sodium to exchangeable sodium in patients with diuretic-induced hyponatremia [13]. Diuretic-induced hyponatremia in these patients is thought to be due to hypokalemia-induced hyponatremia due to the transcellular shift of sodium ions into the cell [13]. According to Eq. 5, the chloride concentration gradient also contributes to the resting membrane potential. Evidence for the contribution of the chloride concentration gradient to the resting membrane potential is demonstrated in an experimental mouse model of thiazide-induced hypocalciuria [14]. It has been demonstrated on immortalized mouse distal convoluted tubule cells that thiazide diuretic inhibits cellular chloride entry mediated by apical membrane NaCl cotransport, resulting in a decrease in the intracellular chloride concentration. Since intracellular chloride is above its electrochemical equilibrium, the chloride equilibrium potenial required to maintain the transmembrane chloride concentration gradient will be more negativce due to the decrease in the intracellular chloride concentration. Consequently, the decrease in the intracellular chloride concentration hyperpolarizes the distal convoluted tubule cells towards their potassium equilibrium potential, and this membrane hyperpolarization in turn stimulates calcium entry by the apical membrane, dihydropyridine-sensitive calcium channels [14].

CONCLUSION

In conclusion, current analysis implicitly assumes that the interrelationship between the plasma potassium concentration $[K^+]_p$ and intracellular potassium concentration $[K^+]_{ICF}$ is defined by the Goldman-Hodgkin-Katz equation by inaccurately assuming that the $[K^+]_{pw}$ is equal to the interstitial fluid potassium concentration $[K^+]_{ISF}$. In actuality, changes in the $[K^+]_p$ will lead to an initial alteration in the $[K^+]_{ISF}$ due to re-establishment of Gibbs-Donnan equilibrium. Changes in the $[K^+]_{ISF}$ will in turn result in changes in the $[K^+]_{ICF}$ due to re-establishment of the transmembrane electrochemical potential. In addition, changes in the $[K^+]_{ICF}$ may consequently lead to the transcellular shift of sodium due to perturbation in the transmembrane sodium electrochemical gradient. The quantitative interrelationships of all these factors are defined by Eq.5. Specifically, the transcellular entry of sodium ions in hypokalemia-induced hyponatremia induced by a deficit of intracellular potassium can be mathematically accounted for by this new formula. Lastly and most importantly, this new formula mathematically accounts for the three compartmental distribution of potassium in the body fluids and the role of Gibbs-Donnan equilibrium and transmembrane electrochemical gradient in defining the plasma potassium concentration.

DECLARATIONS

Data Availability

The data (derivation of a new formula defining the quantitative interrelationship between $[K^+]_p$ and $[K^+]_{ICF}$) used to support the findings of this study are included within the article.

Author Contributions

M.K.N. conception and design of research; M.K.N., M-K.N. and DS.N. analyzed data; M.K.N. drafted manuscript; M.K.N., M-K.N. and D-S.N. edited, revised and approved final version of manuscript; M-K.N. and D-S.N. prepared figure.

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