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**TRANSLATIONAL PHYSIOLOGY**

# Quantitative interrelationship between Gibbs-Donnan equilibrium, osmolality of body fluid compartments, and plasma water sodium concentration

**Minhtri K. Nguyen and Ira Kurtz**

*Division of Nephrology, David Geffen School of Medicine at UCLA, Los Angeles, California*

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**Nguyen, Minhtri K., and Ira Kurtz.** Quantitative interrelationship between Gibbs-Donnan equilibrium, osmolality of body fluid compartments, and plasma water sodium concentration. *J Appl Physiol* 100: 1293–1300, 2006. First published December 15, 2005; doi:10.1152/japplphysiol.01274.2005.—The presence of negatively charged, impermeant proteins in the plasma space alters the distribution of diffusible ions in the plasma and interstitial fluid (ISF) compartments to preserve electroneutrality. We have derived a new mathematical model to define the quantitative interrelationship between the Gibbs-Donnan equilibrium, the osmolality of body fluid compartments, and the plasma water $Na^+$ concentration ($[Na^+]_{pw}$) and validated the model using empirical data from the literature. The new model can account for the alterations in all ionic concentrations ($Na^+$ and non-$Na^+$ ions) between the plasma and ISF due to Gibbs-Donnan equilibrium. In addition to the effect of Gibbs-Donnan equilibrium on $Na^+$ distribution between plasma and ISF, our model predicts that the altered distribution of osmotically active non-$Na^+$ ions will also have a modulating effect on the $[Na^+]_{pw}$ by affecting the distribution of $H_2O$ between the plasma and ISF. The new physiological insights provided by this model can for the first time provide a basis for understanding quantitatively how changes in the plasma protein concentration modulate the $[Na^+]_{pw}$. Moreover, this model defines all known physiological factors that may modulate the $[Na^+]_{pw}$ and is especially helpful in conceptually understanding the pathophysiological basis of the dysnatremias.

plasma water sodium concentration; hyponatremia

IT IS WELL RECOGNIZED THAT the plasma water $Na^+$ and $Cl^-$ concentrations and interstitial fluid (ISF) $Na^+$ and $Cl^-$ concentrations are different despite the high permeability of $Na^+$ and $Cl^-$ ions across the capillary membrane, which separates these two fluid compartments (23). This difference in ionic concentrations between the plasma and the ISF is attributed to the much higher concentration of proteins in the plasma compared with the ISF. Proteins are large-molecular-weight substances and therefore do not cross the capillary membrane easily. The low protein permeability across capillary membranes is responsible for causing ionic concentration differences between the plasma and ISF and is known as the Gibbs-Donnan effect or Gibbs-Donnan equilibrium (23).

Negatively charged, nonpermeant proteins present predominantly in the plasma space will attract positively charged ions and repel negatively charged ions (23). The passive distribution of cations and anions is altered to preserve electroneutrality in the plasma and ISF. As a result, the diffusible cation concentration is higher in the compartment containing nondiffusible, anionic proteins, whereas diffusible anion concentration is lower in the protein-containing compartment. Gibbs-Donnan equilibrium is established when the altered distribution of cations and anions results in electrochemical equilibrium. It is also well recognized that another consequence of the Gibbs-Donnan effect is that there are more osmotically active particles in the plasma space than in the ISF at equilibrium (13, 23). Consequently, the plasma osmolality is slightly greater than the osmolality of the ISF and intracellular fluid (ICF). Indeed, the plasma osmolality is typically 1 mosmol/l $H_2O$ greater than that of the ISF and ICF (13). In addition to the modulating effect of Gibbs-Donnan equilibrium on the $[Na^+]_{pw}$ and plasma osmolality, alterations in the osmolality of the ISF and ICF will also lead to changes in the $[Na^+]_{pw}$ and plasma osmolality due to intercompartmental $H_2O$ shift since the body fluid compartments are in osmotic equilibrium. Presently, there are no formulas in the literature that have determined the mathematical relationships between Gibbs-Donnan equilibrium, osmolality of body fluids (plasma, ISF, and ICF), and $[Na^+]_{pw}$. In this article, based on the principles of Gibbs-Donnan and osmotic equilibrium, we derive for the first time a new equation that quantitatively predicts the effect of changes in negatively charged plasma proteins on the osmolality of all body fluid compartments and the $[Na^+]_{pw}$.

## MATHEMATICAL DERIVATION

### *Quantification of the Effect of Gibbs-Donnan Equilibrium on the $[Na^+]_{pw}$ by Modulating the Osmolality of the Body Fluid Compartments*

It is well known that the plasma osmolality is slightly greater than the osmolality of the ISF and ICF owing to the Gibbs-Donnan equilibrium (13, 23). The plasma osmolality is typically 1 mosmol/l $H_2O$ greater than that of the ISF and intracellular compartment (13).

Therefore: plasma osmolality > total body osmolality

To equate plasma osmolality to the total body osmolality, one has to introduce a correction factor for the incremental effect of Gibbs-Donnan equilibrium on the plasma osmolality. This correction factor, which will be termed *g*, is equal to the ratio of plasma osmolality/total body osmolality and is therefore unitless.

Address for reprint requests and other correspondence: M. K. Nguyen, Division of Nephrology, David Geffen School of Medicine at UCLA, 10833 Le Conte Ave., Rm. 7-155 Factor Bldg., Los Angeles, CA 90095 (e-mail: mtnguyen@mednet.ucla.edu).



  