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Review

Water in the human body: An anesthesiologist's perspective on the connection between physicochemical properties of water and physiologic relevance

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ABSTRACT

The unique structure and multifaceted physicochemical properties of the water molecule, in addition to its universal presence in body compartments, make water a key player in multiple biological processes in human physiology. Since anesthesiologists deal with physiologic processes where water molecules are critical at different levels, and administer medications whose pharmacokinetics and pharmacodynamics depend on interaction with water molecules, we consider that exploration of basic science aspects related to water and its role in physiology and pharmacology is relevant to the practice of anesthesiology. The purpose of this paper is to delineate the physicochemical basis of water that are critical in enabling it to support various homeostatic processes. The role of water in the formation of solutions, modulation of surface tension and in homeostasis of body temperature, acid-base status and osmolarity, is analyzed. Relevance of molecular water interactions to the anesthesiologist is not limited to the realm of physiology and pathophysiology. Deep knowledge of the importance of water in volatile anesthetic effects on neurons opens a window to a new comprehensive understanding of complex cellular mechanisms underlying the practice of anesthesiology.

1. Introduction

The Greek philosopher Thales of Miletus (640-546 aC) observed the universal character of water. He believed that water was the fundamental element that originated the world as we perceive it: “All things are from water and all things are resolved into water” [1]. The ubiquity of water has always been evident, and is remarkable that it is the only substance in nature present simultaneously in three different states of the matter: solid, liquid and gas [2].

The main constituent of living beings is water, which is recognized as the universal solvent [2]. Almost every physiologic process is somehow linked to the presence of water. Fasting that does not include water puts survival at risk in a longer period compared to complete water deprivation. Only the immediate need for air exceeds water necessity [3].

Water is implicated in diverse biomolecular processes. Significant efforts have been carried out in order to elucidate the mechanisms underlying the interaction of water with other substances in these processes, including protein folding and stability as well as enzyme-substrate interactions [4]. Because of its unique properties, such as high specific heat and the ability to dissolve polar substances, water is essential for thermoregulation, transport, and excretion of endogenous and exogenous substances, and is an ideal *milieu* to facilitate many biochemical reactions.

This paper focuses on the identification of the molecular properties of water that are critical in enabling it to support various homeostatic processes. Based on the description of molecular aspects of water, analysis of its role in conformation of biological solutions, thermal and osmolar homeostasis and transport of polar substances as well as the role of water in surface tension in human physiology will be conducted. The role of water on acid-base balance and the impact of water on pharmacokinetics and pharmacodynamics as well as its relevance to the anesthesiologist will also be presented.

2. The water molecule

The chemical structure of water consists of one oxygen atom covalently bound to two hydrogen atoms. The oxygen atom has eight electrons, distributed on the orbital configuration $2s^2\ 2p_x^2 p_y p_z$, that binds two hydrogen atoms with one electron each. The resultant electronic distribution is irregular allowing the electronegative oxygen atoms to attract electrons from both covalent bonds, concentrating the

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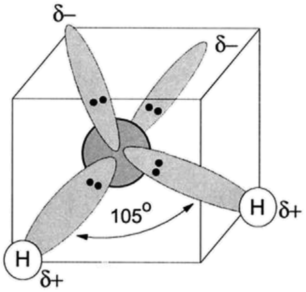

Fig. 1. Water molecule: Lobulated orbital configuration. H, hydrogen atom; δ-, negatively charged lobule. δ+, positively charged lobule available to react with negative lobes from other water molecules.

highest electronic density (negative charge) around the oxygen atom, and the lowest density (positive charge) close to the hydrogen atoms. The electrical charge of the molecule is neutral with eight electrons forming four pairs of hybrid orbitals. The tetrahedral orbital configuration is stable and facilitates that two orbital lobes establish O—H bonds through shared electrons, while the other two electronegative lobes are available to attract other molecules of water (Fig. 1).

The water molecule is asymmetrical and its electrical charge is not evenly distributed (polar structure) [5]. The property of polarity leads to attraction between water molecules through binding of relatively positive hydrogen atoms and the slightly electronegative oxygen atom. The attraction force between water molecules is determined by the high energy contained in the O—H bond of 5.5 Kcal/mol and the Van der Waals interaction [6]. The H—O—H angle is intermediate between a tetrahedral geometry and the angle of a planar pentagon. The average of 104,5° within the molecule (Fig. 2) takes into consideration the distinct geometrical configurations during different modes of vibration, given that the water molecule is not constantly on a zero-point motion situation [7]. The H—O—H angle is a key determinant of polarity that translates into strong interaction between water molecules. Furthermore, this interaction is responsible for the high boiling point and specific heat of water, illustrating the high energy necessary to break H—H bonds. This situation explains the paradox that water is in the liquid state at a wide range of temperatures favorable for physiological processes and not as a gas as would be predicted given its low molecular weight [8].

3. Role of water in physiologic solutions

Human cells are complex systems whose structure and function depend largely on non-covalent interactions not involving creation or rupture of chemical bonds. Protein folding and aggregation, ligand-enzyme interactions, transcription and replication of information polymers, transmembrane ion transport, signal transduction and regulation of gene expression are examples of these non-covalent bonds. A characteristic of non-covalent interaction is the moderate energy range of operation, flexible enough to be efficient and to avoid irreversibility of biochemical reactions. In this context, the solvent is not only a diffusion medium but also a mediator of non-covalent interactions [9].

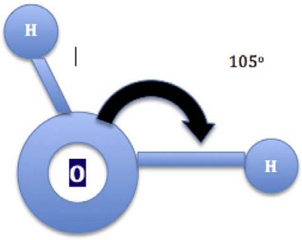

Fig. 2. Tetrahedral angle of water molecule on a zero-motion mode.

Water as the main solvent in fluid compartments, establishes three types of non-covalent interactions: electrostatic, van der Waals and solvent-induced [10]. These non-covalent interactions rule the conformation of solutions when water is in contact with polar, ionic and hydrophobic solutes.

Polar liquids, such as water, are excellent solvents able to participate in solutions by the interaction with other polar substances or ionic materials. Ionic materials dissociate in water, displaying a wide range of physiologic possibilities that range from acid-base homeostasis to transmembrane transport and excretion of substances. When an ionic substance and water are combined in a solution, the electrostatic interactions are reduced in strength in inverse relation to the dielectric constant of water, to the range of other non-covalent interactions [11]. Furthermore, the high dielectric constant of water is critical to avoid formation of strong electrostatic interactions that would render physiologic processes such as signaling and nerve transmission ineffective. Ion-water interactions are involved in biological activities like conformation of proteins, electrostatic potentials, conductances and transmembrane transport [12]. An ionic solute is able to perturb the dynamics of water when participating in solution, while at the same time, this perturbation generates a field that reacts back modulating and altering the solute [13]. This bidirectional effect plays an important role in formation of solutions with hydrophobic substances, through interaction of water with kosmotropes and chaotropes [14]. Kosmotropic cosolvents (Ca^{2+}, Mg^{2+}), when added to water, promote aggregation of hydrophobic solute particles, whereas chaotropic solvents (Cl^{-}, K^{+}, NH_4) destabilize such aggregates [15].

The hydrophobic effect, defined as the tendency of non-polar molecules to aggregate and separate themselves from water when found in solution, has biological implications, including formation of cell membranes, protein folding, formation of micelles and adsorption of proteins into lipid layers. Hydrophobic effects are key factors in cell organization and homeostasis that cannot be substituted for by electrostatic or van der Waals forces [11]. A hydrophobic solute alters the structure of water and decreases entropy (degree of thermodynamic disorder of the system) due to stronger bond formation between water molecules around the solute. To minimize the effect of the hydrophobic solutes on water, such solutes aggregate in a smaller surface area inside a "cage" of solvent, maximizing the amount of free hydrogen bonds in water available to interact with other water molecules [16]. Of particular importance is the impact of the hydrophobic effect on protein stability and the effect of ions and salts on protein solubility in water. Protein molecules have their hydrophobic groups in contact with each other and out of contact with water. The force supporting the structure of proteins is not the weak association of their hydrophobe groups, but the repulsion of such groups out of the water medium [17]. Hydration of proteins occur in a ratio of 1.4–4 g of water per gram of protein, so that approximately 80% of body water is bound to macromolecular components [18]. Body compartment formation is the result of the constant interaction of proteins, and ions dissolved in water, separated by membranes by virtue of hydrophobic effects. In 1888, Hofmeister reported that salts affect solubility of proteins in water [12]. This phenomenon has been interpreted as a modulating effect of salts on hydrophobic effects. The physiologic relevance of this physicochemical feature is poorly understood but it might be involved in the effect of different electrolytic solutions used in clinical practice [19]. On the other hand, structured water molecules determine the thermodynamics of binding of ligands to protein receptors, highlighting the central role that water plays in cellular signaling and pharmacodynamics of medications [20].

Finally, van der Waals bonds are forces that keep water together in the liquid state at temperatures below the boiling point. Although the water molecule is electrically neutral, the distribution of charge within the molecule is not symmetrical, creating a dipole moment. This leads to net attraction between poles, creating cohesion [21]. The physiological significance of van der Waals forces is illustrated by their role in