



## Physiology of aging

Jung Y. Hahr

Children's Hospital of Wisconsin, 9200 W. Wisconsin Avenue, Milwaukee, WI 53226, USA



### ABSTRACT

In a natural state, death of the neuronal cells of the central nervous system is a hallmark of the aging process and occurs very insidiously. As we age, a natural loss of the body water occurs simultaneously with a rise in plasma osmolality. When a progressive rise in plasma osmolality occurs with age, it increases the effective viscosity of the circulating blood, and the thickened blood fails to perfuse the body systems and organs. If red blood cells fail to perfuse the central nervous system, the neuronal cells die from hypoxia and a lack of essential nutrients. This process is insidious but unavoidable. Hyperosmolality occurs in all mammals and it is a natural phenomenon of mammalian aging.

### Introduction

A gradual rise of plasma osmolality is synonymous with the aging process. Modern affluent Western lifestyles, coupled with a naturally occurring deterioration of the body's hormonal balance have accelerated an increase in plasma osmolality in the geriatric population. Researchers have previously observed that memory loss associated with Alzheimer's disease is the same as in the natural aging process, only considerably accelerated.

The ability to maintain oxygen homeostasis is essential for the survival of all living species. The physiological systems that ensure optimal oxygenation and energy supply for all cells in a living organism involve complex anatomical and physiological infrastructures that are present in all living things. Under physiological conditions, an adequate supply of oxygen is adequately provided by maintaining adequate circulation. However, if blood flow cannot be adequately provided, massive cell death and brain damages results. In aged individuals, the gradual rise in plasma osmolality increases the viscosity of the circulating blood, leading to gradual perfusion failure of the red blood cells and a resulting failure to deliver oxygen and essential nutrients.

Reinhart et al. [14] observed that changes in plasma osmolality lead to either swelling or shrinking of the red blood cells (RBCs); they additionally observed the influence of osmolality on the suspension and biophysical properties of RBCs and their ability to perfuse an artificial microvascular network (AMVN). These authors also observed the highest perfusion rate to be at an osmolality of 290 mosm/kg H<sub>2</sub>O and that the perfusion rate decreased as osmolality increased.

### Discussion

Scientists are generally in agreement that at the end of our life, the neuronal cells die from a lack of oxygen and energy [11,12]. Circulation

failure regardless of cause will induce hypoxia and fail to deliver the necessary nutrients to sustain life. Osmolality increases occur at the end of all mammalian life. The gradual rise of osmolality induces circulation failure by thickening the blood which result in perfusion failure that occurs in the brain and all other vital organs.

In human infant, at age one, 70% of the body composition is water, however, by age 60, water accounts for only 60% of the overall body weight [16]. The average human extracellular fluid volume is 5000c.c.–6000c.c. However, the actual water content is approximately 55% of the extracellular fluid volume, because of approximately 45% of the blood is the hematocrit. Therefore, the actual water volume is 2750c.c.–3300c.c. of the total extracellular fluid volume. If one drinks a glass of water (224c.c.), he replenishes approximately 8% of the total 2750c.c. of extracellular fluid volume immediately. As we lose approximately 10% of body weight by age 60, if we replace 8% of the extracellular water volume by drinking a glass of water, that makes our plasma osmolality level reduce to the equivalent of a younger person. Drinking a glass of water contributes to significant blood composition change as well, even it is temporally, as it changes not only the plasma osmolality but also almost every component of the blood reverting to the levels of a younger individual. The above illustration is only for demonstration purposes, and actual physiology could differ somewhat. In the above demonstration, I have used water, however, you could drink coffee, tea or soda in place of water, as they are all flavored water and would have same effects.

In a previous study, when infants were breast-fed, their plasma osmolality was 284.3 mosm/kg H<sub>2</sub>O and when infants were bottle-fed, their plasma osmolality was 293.8 mosm/kg H<sub>2</sub>O at three month of age [4]. These findings indicate that when plasma osmolality is artificially increased as in bottle-fed infants, aging occurs much faster, which is why bottle-fed infants are larger and heavier than their breast-fed peers. As we age, we do not grow but rather age prematurely in older

E-mail address: [jyhahr@att.net](mailto:jyhahr@att.net).

<https://doi.org/10.1016/j.mehy.2018.12.016>

Received 4 October 2018; Accepted 22 December 2018

0306-9877/© 2018 The Author. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

individuals. When we lose body water naturally, the rise in plasma osmolality is natural and unavoidable. When plasma osmolality is increased, the viscosity of the circulating blood increases and the tissue permeability of the circulating the red blood cells decreases. When intravascular viscosity is increased in the brain, intravascular and intracranial pressure increases to maintain adequate circulation, which increases intravascular resistance. Tissues perfusion decreases as intravascular resistance increases and tissues affected by perfusion failure die from a lack of oxygen and the essential nutrients. In the end, progressive neuronal cell deaths, and tissue perfusion failure result as osmolality further increases.

Early effects of hypoxia on neuronal cell function produced by an early cessation of electrical activity, caused by a K<sup>+</sup> conductance-mediated neuronal hyperpolarization and disappearance of excitatory synaptic potentials, can be considered a protective mechanism that prevents the cellular damage resulting from severe mismatch between energy needs and supplies. These changes are triggered by such hypoxia-induced signals as a rise in cytoplasmic free calcium, a decrease in adenosine triphosphate(ATP) level, and extracellular accumulation of adenosine. Upon reoxygenation, the suppression of neuronal /synaptic activity is reversible, as long as hypoxic neuronal cells have an adequate supply of glucose. However, if sufficient ATP cannot be obtained by anaerobic glycolysis to maintain essential Na-K pump activity and protein synthesis, long term cell function and survival are compromised. Thus, when both oxygen and glucose are deficient, the available cellular protective mechanisms cannot prevent the lethal effects of Ca<sup>2+</sup> + influx (Krnjevic, [12]).

As the perfusion rate of red blood cells decreases due to an increase in osmolality, the actual oxygen-carrying capacity of hemoglobin is reduced as well. Both the reduced tissue perfusion of the RBC's and the reduced oxygen-carrying capacity of hemoglobin cause hypoxia in the brain tissue, and concurrently the tissue is deprived of necessary nutrients as perfusion fails. As the perfusion rate decreases, the tissue becomes more acidic and the oxygen carrying capacity of the red blood cells decreases further (i.e. Bohr effects). The PO<sub>2</sub> level also decreases and the oxygen-hemoglobin affinity decreases. Thus, neuronal cell death occurs as the RBCs fail to deliver oxygen and essential nutrients become scarce as stated by Krnjevic [12] and Jha et al. [11].

In the natural aging process, the neuronal cell deaths is slow and confined to a minute area; this is an insidious process, but eventual and progressive neuronal cell death is inevitable.

The normal plasma osmolality range in human is 275 mosm/kg H<sub>2</sub>O to 295 mosm/kg H<sub>2</sub>O, although a  $\pm 10$  mosm/kg H<sub>2</sub>O osmolality gap can result in values up to 305 mosm/kg H<sub>2</sub>O—the accepted upper range for human osmolality. As we age, plasma osmolality increases with the natural reduction of body water. Consequently, the viscosity of the circulating blood increases, resulting in a gradual decrease in tissue perfusion as Reinhart et al. [14] observed. Failure of the red blood cells to perfuse occurs as the plasma osmolality increases and the plasma osmolality level of 310 mosm/kg H<sub>2</sub>O, is the accepted cutoff line representing a medical emergency in human according to the University of Iowa osmolality gap calculator. At this level of plasma osmolality, the permeability of the RBC's is severely reduced, which limits the delivery of the essential oxygen and nutrients necessary for survival. As Reinhart et al. [14] observed the optimal perfusion rate was at a plasma osmolality of 290 mosm/kg H<sub>2</sub>O; thereafter, the perfusing rate gradually decreased as plasma osmolality increased. Plasma osmolality of 290 mosm/kg H<sub>2</sub>O is equivalent to isotonic tonicity.

According to the United States Department of Agriculture(USDA) National Agriculture Library Daily Recommended Intake(DRI table), the protein needed for men aged 19–70 years is 0.66 g/kg/d. This amount is equivalent to only 9% of daily caloric requirements and is necessary for protein homeostasis. Dimeski et al. [5] reported that at a plasma protein level at the upper range of normal (7.8–8.3 g/l), we lose extracellular sodium. As a result, the body cannot retain sufficient water leading to higher plasma osmolality. Sodium and protein

peptides are the two major components in the extracellular space that affect plasma osmolality. The total amount of sodium in the body controls the total body fluid level by adjusting the amount of urine excretion. Sodium is responsible for maintaining approximately 280 mosm/kg H<sub>2</sub>O of the 300 mosm/kg H<sub>2</sub>O of plasma osmolality (Dufour, [7]). If there is not enough sodium, our body lose corresponding amount of water immediately, resulting in higher plasma osmolality. Martin et al. [13] studied five men who participated in a 12 week controlled study involving high-protein, moderate-protein and low-protein diets. The baseline plasma osmolality was greater for the high protein diet compared to the lower protein and moderate protein diet.

Prolonged dietary intake of foods high in animal-based protein is associated with higher plasma osmolality, and high plasma osmolality trends are further exacerbated by the natural aging process, which involves reduced androgen, estrogen and AVP secretion, etc. With the natural reduction of all of hormonal secretions, the human body loses its capacity to retain water which further increases the plasma osmolality. Factors conducive to an increase in plasma osmolality include a diet high in animal-based protein [5,9], high alcohol consumption, a lack of physical activity, and inadequate fluid and sodium intakes [9]. These are a few of the factors commonly associated with an increase in plasma osmolality in daily life.

Albert et al. [1,2] observed hyperosmolality in Alzheimer's patients with an average plasma osmolality of  $310 \pm 1$  mosm/kg H<sub>2</sub>O, and in the elderly control group with  $305 \pm 1$  mosm/kg H<sub>2</sub>O and  $313 \pm 4$  mosm/kg H<sub>2</sub>O with the control group  $300 \pm 3$  mosm/kg H<sub>2</sub>O plasma osmolality values after mild fluid restriction overnight. These patients were hospitalized and overtly symptomatic. In this group of patients, the measured osmolality could even exceed 320 mosm/kg H<sub>2</sub>O in a given day; additionally, the osmolality of all these patients was higher than 310 mosm/kg H<sub>2</sub>O. These are not incidental findings and lead to the conclusion that Alzheimer's disease is a disease of hyperosmolality.

Stoohoff et al. [15] observed massive apoptosis of neuroblastoma cells after 30 min exposure to hyperosmotic stress and noted robust increase in tau phosphorylation, indicating aberrant activity associated with neuronal cell deaths.

Protein damage is a consequence of hypertonic stress, and cell hypertonicity decreases cell volume, cell transcription and cell translation. Hypertonicity also increases cell ionic strength, macro molecular crowding, DNA damages and oxidative stress [3].

In the normal aging process, neuronal cells death can be delayed by drinking water, which reduces plasma osmolality and maintains red blood cells perfusion; thus immediate neuronal cells death can be avoided and the normal aging process can be delayed. All of this is possible if the plasma osmolality is reduced. One can accelerate the increase in plasma osmolality and age prematurely, as in Alzheimer's disease, or one can decelerate the rise in plasma osmolality and delay the final inevitability.

When the neuronal cell death occurs due to a normal rise in osmolality, this is the normal aging process, on the other hand, when the neuronal cell death occurs due to an accelerated rise in osmolality, it is considered Alzheimer's disease.

If brain damage is the result of the failure of the red blood cells to perfuse the central nervous system due to high plasma osmolality, then it is possible to prevent the perfusion failure by reducing plasma osmolality. Alzheimer's disease is preventable through a reduction in plasma osmolality, and the normal aging process can be slowed in the same manner.

Researchers [6] have stated that drinking coffee and tea and consuming a Mediterranean diet [10] can help to slow the progression of memory loss. A cup of coffee or tea is mostly water and drinking water reduces plasma osmolality. A Mediterranean diet is low in meat and preserves body sodium, inducing the retention of water, and resulting in lower plasma osmolality.

Fang et al. [8] have advocated that having a high uric acid level, such as in gout, reduces memory loss, but it is not uric acid that improves memory. Gout is a disease of hyperosmolality, when one has an active gout, this implies that person is in a hyperosmotic state which is why that person losing memory. When an individual with gout is advised to eat less meats and drink more water, this in turn reduces plasma osmolality, thereby improving memory. This is a prime example of how plasma osmolality has direct effects on memory. Hyperosmolality harms memory, and lowered plasma osmolality improves memory loss although uric acid itself has no direct effects on memory loss.

Exercise has beneficial effects on memory loss in the human brain. Exercise shortens the lifespan of the circulating red blood cells by removing old red blood cells and producing new, younger red blood cells that have a greater actual oxygen-carrying capacity than the old red blood cells. Furthermore, when exercise levels are increased, the individuals tend to drink more water, which improves the perfusion rate of red blood cells by reducing plasma osmolality. This process is how exercise improves memory.

The brain damages observed in normal aging and in Alzheimer's disease are the same general process and the extent of that damage is dependent on the severity of hypoxia.

In conclusion, the well being of the human body is directly related to plasma osmolality. By improving the perfusion of RBCs and by reducing plasma osmolality, not only can one prevent the progression of Alzheimer's disease but also slow the normal aging process. Under conditions of high plasma osmolality, the brain will have serious signs of stress regardless of patient age.

#### Conflict of interest

None.

#### Funding

None.

#### References

- [1] Albert SC, Nakra BR, Grossbeg GT, Caminal ER. Drinking behavior and vasopressin responses to hyperosmolality in Alzheimer disease. *Int Psychogeriatr* 1994;6(1):79–86.
- [2] Albert SC, Nakra BR, Grossberg GT, Caminal ER. Vasopressin responses to dehydration in Alzheimer disease. *J Am Geriatr Soc* 1989 Sep;37(9):843–7.
- [3] Burg MB, Ferrais JD, Dimitrieva NI. Cellular response to hyperosmotic stresses. *Physiol Rev* 2007;87:1441–74.
- [4] Davies DP. Plasma osmolality and feeding practices of healthy infants in first three month of life. *Br Med J* 1973;2:340–2.
- [5] Dimeski G, Barnett RJ. Effects of total protein concentration on plasma sodium, potassium and chloride measurements by indirect selective electrode measuring system. *Clin Care Resuscitation* 2005;7:12–5.
- [6] Driscoll I, Shumaker SA, Snively BM, Margolis KL, Manson JE, Vitols MZ, Rossom RC, Espeland MA. Relationships between caffeine intake and risk for probable dementia or global cognitive impairment: the women's health initiative memory study. *J Gerontol* 2016;71(12):1596–602.
- [7] Dufour DR. Osmometry. New York N.Y.: American Association for clinical chemistry meeting; 1993.
- [8] Fang P, Li X, Luo JJ, Wang H, Yang XP. A double-edge sword: Uric acid and neurological disorders. *Brain Disord Ther* 2013 Nov 1;2(2):109.
- [9] Hahr JY. Physiology of the Alzheimer's disease. *Med Hypo* 2015;85:944–6.
- [10] Hardman RJ, Kennedy G, Macpherson H, Scholey AB, Pipingas A. Adherence to a Mediterranean-style diet and effects on cognition in adults: A qualitative evaluation and systematic review of longitudinal and prospective trials. *Front Nutr* 2016 Jul;22(3):22.
- [11] Jha NK, Jha SK, Sharma R, Kumar D, Ambasta RK, Pravir K. Hypoxia-induced signaling activation in neurodegeneration: targets for new therapeutic strategies. *J Alzheimers Dis* 2018;62(1):15–38.
- [12] Krnjevic K. Early effects of hypoxia on brain cell function. *Croat Med J* 1999 sep;40(3):375–80.
- [13] Martin WF, Cerundolo LH, Pikosky MA, Gaine PC, Maresh CM, Armstrong LE. Effect of dietary protein intake on indexes of hydration. *J Am Diet Assoc* 2006;106(4):587–9.
- [14] Reinhart WH, Piety NZ, Goede JS, Shevkopyas SS. Effect of osmolality on erythrocyte rheology and perfusion of an artificial microvascular network. *Microvasc Res* 2015 Mar;98:102–7.
- [15] Stoothoff WH, Johnson GV. Hyperosmotic stress-induced apoptosis and tau phosphorylation in human neuroblastoma cells. *J Neurosci* 2001;65(6):573–82.
- [16] Nelson's textbook of Pediatrics. 1996 p. 2050.