Physiology of the Alzheimer's disease

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A R T I C L E   I N F O

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A B S T R A C T

Alzheimer's disease is a disease that is resulted from increased plasma osmolality both the excessive consumption of animal-based proteins and reduction of sodium intake, that resulted to increase plasma osmolality. When we are exposed to high animal-based protein diets throughout life, we gradually lose extracellular sodium and the body cannot retain water, resulting in a gradual rise of plasma osmolality. When the neuronal cells of the central nervous system are exposed to high osmolality stress, they produce of phosphorylated tau, APP, and pathologic beta amyloid protein peptides. The BACE 1 protein which influences the cleavage of amyloid precursor proteins (APP) and affects the production of beta amyloid protein peptides, is also increased in a hyperosmotic stress. When pathologic beta amyloid protein peptides are produced, they are degraded by the ubiquitin proteasome proteolytic pathway, and only then are the neurotoxic effects on the central nervous system manifested, leading to Alzheimer's disease.

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Introduction

Dementia, a syndrome of many causes, reportedly affects more than 15 out of 32 million Americans who are over 60 years of age. It has a total healthcare cost of more than $200 billion annually, according to the Alzheimer's Association report of 2012. This author has reviewed the published literature and discusses for possible physiology of the Alzheimer's disease.

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 of only 9% of total daily calorie requirement and is necessary for protein homeostasis. In today's culture, we are exposed to a large amount of animal-based protein daily. When the plasma protein level is at the upper range of normal, we lose extracellular sodium [8]. As a result the body cannot retain water in the environment of reduced extracellular sodium, leading to higher plasma osmolality. Martin et al. [14] studied five men participated in a 12 week controlled study with high protein, moderate protein and low protein diets. The baseline plasma osmolality was greater for the high protein diet compared to the low protein and moderate protein diet.

The normal ranges of plasma osmolality are 275 mosm/kg in children and 295 mosm/kg in adults [4] and 285 mosm/kg to 295 mosm/kg in adults [12]. Plasma osmolality 295 mosm/kg plus an acceptable osmolality gap (OG) of ±10 mosm/kg is 305 mosm/kg and is an upper limit of normal range. Plasma osmolality 310 mosm/kg is a cutoff line and anything above 310 mosm/kg is considered as a medical crisis, according to the University of Iowa osmolality gap calculator. However, Quest Clinical Laboratory, the nation's largest clinical laboratory, currently reports that their normal range of plasma osmolality is 280–305 mosm/kg.

When the neuronal cells of the central nervous system are exposed to hyperosmotic stress, they induce tau phosphorylation and the production of beta amyloid precursor proteins (APP). BACE 1 proteins influence the cleavage of APP and affect the production of beta amyloid proteins, and they are also increased in the hyperosmotic state [19]. Stoothoff et al. [18] observed that the increased apoptosis of neuroblastoma cells after a 30-min exposure to hyperosmotic stress and hyperosmotic stress also resulted in a robust increase in Tau phosphorylation. Kipfer-Kauer et al. [13] injected a hypertonic saline solution into vein of one eye of three-month-old C57BL/6 mice and observed high APP and beta amyloid protein peptides in the eye that was injected with the hypertonic saline solution after 6 weeks. Tan et al. [19] observed increased beta-site APP cleaving enzyme 1 (BACE1) activities and concentrations in response to mild oxidative stress. APP were found in the brains of human newborn infants that were exposed to perinatal hypoxic injury [3]. Increased tau phosphorylation, APP production and pathogenic beta amyloid protein peptides are the hallmarks of the neuronal cells of the central nervous system that are exposed to stress, regardless of the type of stress and they are not an indication of Alzheimer's disease.
In the reported studies on Alzheimer’s disease, all of the Alzheimer’s disease patient groups had higher plasma osmolality at 310 ± 1 mosm/kg and 313 ± 4 mosm/kg than the non-Alzheimer’s disease control patient groups at 305 ± 1 mosm/kg and 300 ± 3 mosm/kg after a mild overnight fluid restriction [1,2].

Discussion

Albert et al. [1] observed hyperosmolality in all of the Alzheimer’s disease groups after a mild overnight fluid restriction. The disease groups showed 310 ± 1 mosm/kg and 313 ± 4 mosm/kg plasma osmolality and they experienced a greater degree of dehydration, compared to the controls at 305 ± 1 mosm/kg and 300 ± 3 mosm/kg. This indicates that Alzheimer’s disease patient groups did not have adequate sodium to retain body water, if they had retained additional sodium, the Alzheimer’s disease patient groups would not have been dehydrated, indicating they needed additional sodium for proper fluid and electrolytes homeostasis.

Normal acceptable range of osmolality gap (OG) is −10 to +10 mosm/kg H2O, this makes 295 mosm/kg plus osmolality gap of 10 mosm/kg is 305 mosm/kg as an upper limit of normal plasma osmolality, plasma osmolality should never exceed 300 mosm/kg plus osmolality gap of 10 mosm/kg, plasma osmolality of 310 mosm/kg is the crisis point and anything above this is in a medical emergency according to the University of Iowa osmolality gap calculator.

We all consume far more animal-based proteins than is required to maintain homeostasis. Normal range of plasma osmolality is 275 mosm/kg to 295 mosm/kg [4] and [12], Quest Critical Laboratory indicated that their normal range of plasma osmolality is 280–305 mosm/kg and with osmolality gap of 10 mosm/kg, that makes plasma osmolality 315 mosm/kg. This indicates a large number of population has this range of plasma osmolality and this is beyond the point of medical emergency. If this is any indication of the current state of human health, we are in a grave situation and we are going to see massive number of dementia in the near foreseeable future.

Albert et al.’s [1,2] Alzheimer’s disease patient group, as a group their plasma osmolality between 310 ± 1 and 313 ± 4 mosm/kg, they were overtly symptomatic, debilitated and were profoundly affected. Alzheimer’s disease is a very insidious and progressive disease, and the disease process started long before their plasma osmolality reached 310 ± 1 mosm/kg.

Osmotic homeostasis is fundamental for most cells, because they experience recurring alternations in environmental osmolality that challenge cell viability. Protein damage is a consequence of hypertonic stress, and cell hypertonicity decreases cell volume, transcription and cell translation. Hypertoncity also increases cell ionic strength, macromolecular crowding, DNA damages and oxidative stress [5]. Hypertonic stress increases aggregation and the misfolding of diverse proteins in multiple cell types and protein damage is rapid [6]. Degradation of misfolded and damaged proteins is performed principally by the ubiquitin proteasome pathway and autophagy (Nunes et al. 2011). However autophagy is not involved in the removal of pathogenic beta amyloid protein peptides in the Alzheimer’s disease [16].

The daily recommended allowance of proteins is 10–15% of the daily total caloric requirement, and chronic exposures to high protein diets induces high plasma osmolality by reducing extracellular sodium. When the amount of proteins in the extracellular space is in the upper level of the normal range, this results in a loss of sodium in the extracellular space [8], and consequently, our bodies cannot retain body water. This loss of sodium exacerbates the natural loss of body water in old age and high plasma osmolality ensues. Among the many possible source of stress that can harmfully influence the neuronal cells of central nervous system, high protein diets is more frequent and repeated offending agents, the high protein diets is not only cause of reducing extracellular sodium, but high serum lipid and high glucose level can also induce reduction of the extracellular sodium [9,7] that results in a high plasma osmolality. It is well established that increased incidences of Alzheimer’s disease among the patients of hyperlipidemia and diabetic patients.

In general, many of working men and women are having only two regular meals daily and these may not be sufficient electrolytes intake daily to maintain electrolyte homeostasis, furthermore, by dieting to control body weight, large number of men and women undergo repeated dieting, in dieting they typically drink water only without any other consideration, our bodies need water as well as all the electrolytes for daily maintenance. When we are not replenished body sodium during dieting process, our body cannot retain the water, resulting in a significant water loss. Our body adjust by increasing plasma osmolality, this is very harmful practices and this results in a gradual rise of the plasma osmolality. Not sufficient sodium intake is coupled with large amount of animal-based proteins we consume that reduces extracellular sodium, resulting in a high plasma osmolality, exposing the neuronal cells of the central nervous system to hyperosmotic stress.

Sodium and protein peptides are the two components in the extracellular space that strongly affect plasma osmolality. The total amount of sodium in the body controls the amount of total body fluid by adjusting the amount of urine excretion, sodium is responsible for 280 mosm/kg of 300 mosm/kg of plasma osmolality [10].

The function of tau proteins is to stabilize microtubules when microtubule remodeling occurs after neuronal cells are exposed to stress [17], Stoothoff et al. [18] observed that tau phosphorylation was an immediate reaction within a few hours after exposure to hypertonic stress. Amyloid precursor proteins (APP) were found in the brains of human newborn infant that were exposed to perinatal hypoxic injury [3]. Baiden-Amissah et al. noted immunohistochemical changes within 24 h of injury, and APP activity was greatest in the infants who died within three days. This result indicates that the formation of APP takes slightly more time than tau phosphorylation after exposure to stress. Kipfer-Kauer et al. [13] observed high levels of APP and amyloid protein peptides 6 weeks after exposure to a hypertonic saline solution. Furthermore, Tan et al. [19] observed increases in the BACE1 activity and protein concentration in response to mild oxidative stress.

APP, beta amyloid protein peptides and BACE 1 are a hallmark of neuronal cells that have been exposed to stress and they are not an indication of Alzheimer’s disease. When we are young, APP is cleaved by alpha-secretase, and it aggregates and form neurofibrils and neurofibrillar plaques. On the other hand, when we are old, APP produced are cleaved by beta-secretase, leading to the formation of pathogenic beta amyloid proteins. These pathogenic proteins are degraded by the ubiquitin proteasome proteolytic pathway, leading to neurotoxicity in the central nervous system and Alzheimer Disease. The alpha-secretase and Beta-secretase activities are fully age-dependant [15].

If Alzheimer’s disease is the result of pathologic beta amyloid protein peptides produced in the central nervous system, which are degraded by the ubiquitin–proteasome proteolytic pathway [11], then it should be possible to prevent Alzheimer’s disease by increasing water intake, controlling sodium intake, reducing meats consumption, and increasing nitrogen expenditure through exercise. All of these measures will reduce plasma osmolality, even though these are only palliatives. Increased water intake with increased sodium consumption is mandatory to reduce plasma osmolality because the normal thirst mechanism is not functional in patients with high plasma osmolality [1,2]. The protective thirst
mechanism does not trigger until their osmolality has risen to very high levels. Therefore, patients with high plasma osmolality, should not rely on thirst mechanism to induce water drinking. By doing so, they are risking exposing neuronal cells of their central nervous system to hyperosmotic stress.

If patients with cardiac ailments are healthier with serum sodium level of 138 meq/L than patients with serum sodium levels of 145 meq/L, those patients with serum sodium levels 138 meq/L will have lower plasma osmolality and their hearts will be much less strained while maintaining circulation than patients with serum sodium levels of 145 meq/L. A serum sodium level of 138 meq/L is not a reflection of the total body sodium contents, it is merely a reflection of the ratio between serum sodium and water molecules at a given time. Actually patients with serum sodium levels of 138 meq/L have more sodium than patient with serum sodium levels 145 meq/L. When patients have more total body sodium, they retain more water and show reduced serum sodium levels to the body water content.

Conflict of interest

None existed.

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References