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Review Article

The Central Nervous System and its Oxygen Content. Implications in the Context of Neurodegenerative Diseases

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Abstract

Behavior and cognitive functions are results of a fine tuning of multiple neuronal synapsis and a myriad of biochemical reactions whose number, location, components, sequence, and logic are unknown.

In entirely theoretical terms deleterious effects of reactive oxygen species (ROS) production during aerobic metabolism are neutralized by the antioxidant systems and in this manner the brain effectively regulates its oxygen consumption and redox generation capacity.

The knowledge about the metabolic processes of the CNS is so elementary, so theoretical, that only in the previous paragraph we find two notable errors: aerobic metabolism and oxygen consumption.

The phrase aerobic metabolism refers to the fact that the oxygen contained in any tissue of the human organism, such as the CNS, comes from the air that surrounds us, since it is supposedly absorbed through the lungs and reaches the bloodstream to be distributed to all the cells of the organism.

However, since 1850 researchers of the stature of Christian Bohr, Carl Ludwig, and Halender, published works in which, according to their experiments, the diffusion of atmospheric oxygen through the pulmonary alveoli could not explain the enormous difference between the concentration of atmospheric oxygen, which ranges between 19 and 21%, and the % SpO_2 in the blood that reaches values of 98 and 99% [1].

It was precisely the search for the mechanism that would explain such a difference between oxygen in the atmosphere and blood oxygen, which led these researchers to publish that there was no such thing, and that diffusion alone did not explain such a difference.

Unfortunately, at that time, the work of Krogh appeared [2] who, by means of a theoretical mathematical model, apparently simple, explained the unlikely passage of atmospheric oxygen to the bloodstream through the pulmonary alveoli. Krogh's lung gas exchange model has been the foundation of respiratory physiology for the past 100 years even though the mathematical concepts it handles are so far-fetched that they cannot even be experimentally contrasted.

Krogh's original model has been modified and something like 100 equations have been added to try to explain the supposed passage of atmospheric oxygen to the bloodstream through the pulmonary alveoli, but even so, the experimental results do not square with the predictions of such a model. So, research and care for patients during the past 100 years has been based on eminently theoretical models.

So, returning to the phrase "aerobic metabolism of the CNS", we have the surprise that it is wrong because the oxygen we have inside the body does not come from the air that surrounds us but from the water that contains inside each cell that conforms us.

Keywords: Oxygen; aerobic; Krogh´s model; energy; combustion; CSF

The aerobic metabolism of the Central Nervous System

Briefly: the oxygen normally present in the CNS tissues coming from atmosphere and the cells using it to combine with glucose to get energy. But as we discussed in the previous paragraphs, oxygen from the atmosphere can hardly pass through the pulmonary alveoli and reach the bloodstream.

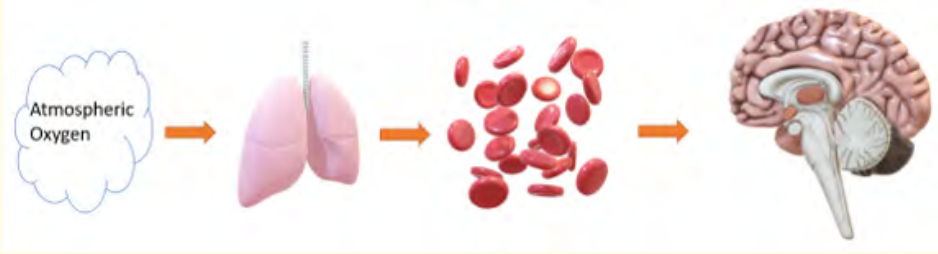

Figure 1: Current concepts about oxygen transportation. It can be considered as a dogma given the implied mechanisms are poorly understood.

It is important to determine the origin of this oxygen, especially at the high levels found inside living beings. So, we have that the lung does not absorb oxygen from the air, and on the other hand we have that our body is able to take oxygen from the water it contains, like plants [3].

Therefore, they are fundamental errors on which the theoretical biochemistry of the CNS metabolism is based, on the one hand, this oxygen does not come from the air, but from water, and on the other hand, our body, when taking the oxygen from the water contained in the cells, at the same time obtains energy, which is transported by the hydrogen that is released when dissociating the water.

The reaction would be as follows:

$$H_2O_{(liq)} \rightarrow 2H_{2(gas)} + O_{2\,(gas)} \rightarrow H_2O_{(liq)} + 4e^-$$

Unlike plant chlorophyll (and hemoglobin), where the dissociation of water is irreversible, and is written as follows:

$$H_2O_{(liq)} \rightarrow 2H_{2\,(gas)} + O_{2\,(gas)}$$

Hemoglobin can dissociate irreversibly the water molecule.

So, when under the right conditions we measure the oxygen content of hemoglobin, it will always have a very high % SpO_2, of more than 95%, But it is because hemoglobin constantly produces oxygen, given it dissociates it incessantly, day and night.

And to date, based on wrong assumptions, such as Krogh's model, we thought that oxygen was carried by hemoglobin, which attributes to hemoglobin a passive role, when in fact it generates oxygen (and hydrogen) by dissociating the molecule from water, so hemoglobin is a far cry from being a molecule that passively transports gases.

Oxygen is a molecule with high toxicity, but nature has optimized its function over eons of years of evolution, as it has gone from a necessary evil to an indispensable element for life, because when water dissociates, hydrogen and oxygen are produced at the same time, both in molecular form. But the valuable in terms of energy is hydrogen, and oxygen performs other functions, but not as a source of energy, for example when combined with glucose.

For instance, the greatest danger faced by divers who use oxygen-enriched gas mixtures is central nervous system oxygen toxicity (CNS-OT). CNS-OT is characterized by convulsions resembling grand-mal epileptic seizures, which may terminate in drowning and death [4].

CNS-OT is characterized by tunnel vision, tinnitus, headache, nausea, dizziness, and twitching of the muscles of the face. Convulsions like epileptic seizures may also appear, as well as sudden loss of consciousness, sometimes without any warning symptoms [5].

It is interesting the resemblance of CNS-OT symptoms with those of neurodegenerative diseases, i.e., the tunnel vision like in glaucoma, which is very frequent in Alzheimer´s disease and Parkinson disease, not to mention the other symptoms such as dizziness, headaches, ringing of ears, convulsions, muscle spasms, which also frequently accompany degenerative diseases of the central nervous system.

The cellular mechanisms underlying the development of CNS-OT are not understood, and may include reactive oxygen species (ROS), which can oxidize specific cellular components, producing neurochemical alterations that conclude in neurotoxicity [6]. Reactive nitrogen species (RNS) also play a role, [7] as does nitric oxide (NO), which modifies GABA metabolism and may contribute to neuroexcitation and seizures [8].

The correlation between elevated inspired PCO_2 (P_iCO_2) and an increased risk of CNS-OT has been well established in animal models [9]. There are several possible mechanisms poorly understood to try to explain the higher risk of CNS-OT in the presence of elevated levels of CO_2, as cerebral vasodilatation induced by CO_2, suppression of sensitivity of peripheral CO_2 chemoreceptors to H^+, which might lower the potential ventilation rate and result in higher arterial levels of CO_2 [10]. CO_2 may increase the production of NO, which also results in cerebral vasodilatation [11]. Other theoretical mechanism is increased production of peroxynitrite [12], and the possible ROS production in the presence of CO_2/H^+, such as Fenton reaction, might generate hydroxyl molecules [13].

Biochemical integrity of the brain is vital for normal functioning of the central nervous system (CNS). The main factor contributing to cerebral biochemical impairment is a much-commented chemical but poorly defined process called oxidative stress. Oxidative stress occurs upon excessive free radical production resulting from an insufficiency of the counteracting antioxidant response system. The brain, with its high oxygen consumption and lipid-rich content, is highly susceptible to oxidative stress. Therefore, oxidative stress-induced damage to the brain has a strong potential to negatively impact normal CNS functions. Although oxidative stress has historically been involved mainly in neurodegenerative disorders such as Alzheimer disease, Huntington disease, and Parkinson disease, its involvement in neuropsychiatric disorders, including anxiety disorders and depression, is beginning to be recognized [14]. By the way, the brain does not consume oxygen, oppositely, the brain produces it dissociating the water molecule, through various molecules, mainly neuromelanin.

Under normal conditions, deleterious effects of ROS production during aerobic metabolism are neutralized by the antioxidant system and in this manner the brain effectively regulates its oxygen consumption and redox generation capacity. When ROS production exceeds scavenging capacity of antioxidant response system, extensive protein oxidation and lipid peroxidation occurs, causing oxidative damage, cellular degeneration, and even functional decline [15]. Congruously, cellular degeneration and functional decline are often accompanied by hypoxic conditions due to impairment of water dissociation.

Oxygen in the blood

Supposedly, Oxygen is carried in the blood in two forms: (1) dissolved in plasma and RBC water (about 2% of the total) and (2) reversibly bound to hemoglobin (about 98% of the total) [16]. In the liquid phase, diffusion rates of gases are generally 10,000 to 600 000 times smaller than those in gaseous environments due to the much shorter mean free path between collisions with other molecules [17]. The distances over which gas transfer must take place in the liquid phase are generally short (about 100 times shorter than that in the gas phase).

The interpretation of the percentages of oxygen that plasma carries (2%), and the marked difference with hemoglobin (98%), has been interpreted according to Krogh's theory during the past 100 years, but if we interpret these percentages based on the unsuspected ability of hemoglobin to irreversibly dissociate the water molecule, like chlorophyll, [18] then these proportions begin to be congruent, because the plasma does not have molecules that can dissociate water.

Oxygen in the Central Nervous System

The brain, as a very high energy consumer, is completely reliant on molecular oxygen but paradoxically oxygen is dangerous due to tissue toxicity [19]. It seems to be mechanisms to protect the brain under low oxygen conditions. These mechanisms involve systemic and central metabolic and vascular processes that are mediated by hypoxia-inducible factor (HIF)-1. HIF-1-mediated cerebral angiogenesis is completed within 3 weeks of exposure onset and is reversible over the same time frame if Normoxia is restored. Hypoxic acclimatizing responses may be significantly impaired with aging and metabolic or vascular disease.

However, it is not the lack of oxygen that initiates compensation mechanisms, but the decrease in the dissociation of the water molecule. Oxygen is a marker of the turnover rate of water dissociation, by which tissues take oxygen from water and especially hydrogen, which is the molecule that carries the energy that is released by breaking the water molecule. Recall that water dissociation by melanin is in the range of Pico and nanoseconds.

The rate at which it happens and the products that are obtained from the reaction are astonishingly accurate and have not changed since the beginning of time. But when its rhythm, its speed, its frequency, or the products of the reaction are disturbed, the also astonishingly accurate intracellular chemical processes resent it, and sooner or later become disorganized, which is the beginning of any disease.

Nature makes all bodies without error, such is their righteousness, say Chinese philosophers, but the perfect synchrony of water dissociation is lost by air pollution, water pollution, pesticides, herbicides, fertilizers, plastic metals, solvents, industrial waste, food and beverage additives, alcohol, extreme climates, etc. And this imbalance in the very first reaction of life in plants and animals (the dissociation of water) has extensive repercussions and depending on the degree of alteration they become the entire width of the complicated gear of the cell, including the cell nucleus.

There by Central Nervous System oxygen toxicity will not be understood clearly until we take in account that oxygen is mainly an indirect indicator of water dissociation, but not a gas that naturally comes from the atmosphere, and is readily or at least passively absorbed by the lungs, that supposedly reaches the bloodstream whom distributes it to the entire economy, and finally the cell uses it to combine it with glucose or its intermediate metabolites to obtain energy.

The up regulation of hypoxia inducible factors or more precisely its dysregulation is due to the low levels of hydrogen, and not from low levels of oxygen. Therefore, therapies based on anti-VEGF monoclonal antibodies have quiet modest results because they are not going to the bottom of the problem, which is the lack of hydrogen, not directly an oxygen related disease.

The brain, as well as any tissue of the body (figure 2) is embedded in water, so that the exact substrate required by the various molecules that dissociate water in the organism, is always within reach of any cell or neuron.

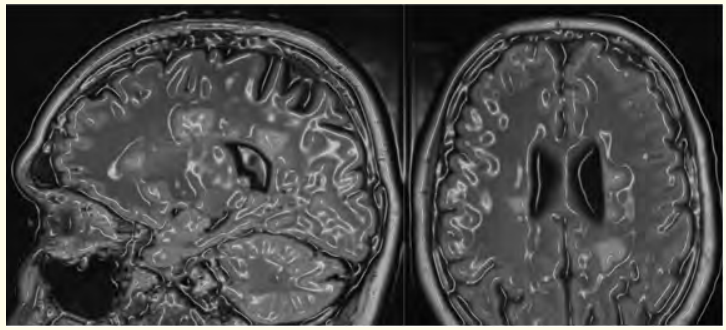

Figure 2: Digitally it is possible to highlight the constant presence of water in all tissues of the body.

An important data about that the turnover rate of water dissociation and reforming is not happening properly is the increase in ventricular volume (figure 3), which is a constant finding in Alzheimer's and other neurodegenerative diseases.

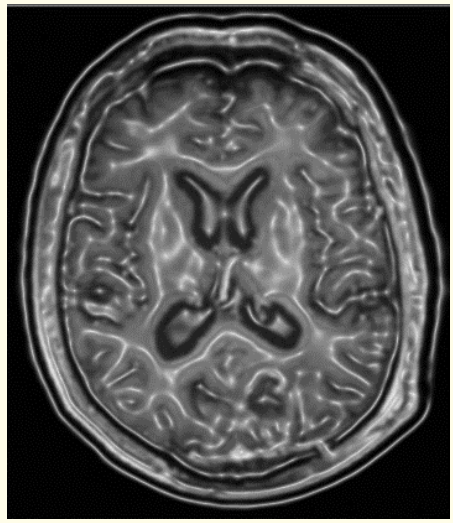

Figure 3: When the appearance of water on the CNS is digitally enhanced, it seems that it easily passes from one CNS compartment to the other. However, it is not so, the passage of water from the cerebrospinal fluid to the CNS tissues as well as its return to the ventricle, is strictly regulated.

The unsuspected ability of neuromelanin to transform light energy into chemical energy, by means of dissociation from water, like plants, explains the formation, reabsorption, and dynamics of the cephalospinal fluid [20].

Therefore, when the volume of the ventricles increases, it is because the water dissociation phase, which by the way is the one that requires the most energy, is not happening properly. That is, water does not separate into its gaseous components and begins to accumulate in the ventricles.

Changes in adjacent neuronal tissue (atrophy, inflammation, fibrosis) are functional and anatomical changes secondary to a lack of oxygen and hydrogen coming from ventricular water dissociation.

Currently, in the clinic, it is interpreted in a totally opposite way because it is thought that first the tissue retracts, and the water of the CSF, in a totally passive role, simply fills the empty space. Which is not the case, because water is the perfect substrate for the various molecules of the human body capable of transforming light energy into chemical energy, through the dissociation of water, like plants.

Conclusion

At last, we can shake off 400 years of dogmas that have perpetuated the erroneous belief that the oxygen we have inside the body comes from the atmosphere. And despite the work of distinguished researchers, the belief continued, perhaps fueled by the lack of a congruent explanation about the origin of oxygen inside the human body.

But just as plants do not absorb oxygen from the air but take it from the water they absorb mainly through the roots, humans and mammals or animals in general extract the oxygen and hydrogen that is metabolically required from the water located inside the cells.

This observation allows us to rule out two erroneous dogmas widespread in a single blow: 1) That our body takes oxygen from the air around us, and 2) that this oxygen combines inside the cells with glucose or its intermediate metabolites, a process called combustion, to obtain energy.

And it is that the wisdom of nature is manifested once again, because by dissociating the water molecule, using light energy, the cells obtain the precious oxygen, but mainly they look for hydrogen since it is the element that carries the energy that is released when dissociating water.

And it is this energy, carried by the smallest atom, that sets in motion the intricate biochemical machinery of the cell. Glucose, which is undoubtedly a fantastic molecule, is only the universal precursor of any organic molecule that makes us up, both in plants and animals, but it is not able to provide the energy that its own metabolism requires.

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