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Global warming and neurodegenerative disorders: speculations on their linkage

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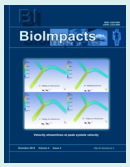

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Summary

Climate change is having considerable impact on biological systems. Eras of ice ages and warming shaped the contemporary earth and origin of creatures including humans. Warming forces stress conditions on cells. Therefore, cells evolved elaborate defense mechanisms, such as creation of heat shock proteins, to combat heat stress. Global warming is becoming a crisis and this process would yield an undefined increasing rate of neurodegenerative disorders in future decades. Since heat stress is known to have a degenerative effects on neurons and, conversely, cold conditions have protective effect on these cells, we hypothesize that persistent heat stress forced by global warming might play a crucial role in increasing neurodegenerative disorders.

Authors Biosketch

George Perry is recognized as the world's leading Alzheimer's disease researcher, specifically in the area of oxidative stress. He has been studying the disease and its effects on the brain for more than 30 years. Dr. Perry's research is primarily focused on how cells in the brain respond to the presence of these free radicals. Looking at how the cells react is like looking through a window into the disease. Dr. Perry is currently working to determine what causes the increased amount of free radicals, and what leads to the damage they cause. Figuring out how the brain's cells respond to free radicals is critical to interrupting the progress of the disease, and could lead to new interventions in patients as young as those in their 30's and 40's.

Morteza Mahmoudi is a Director of NanoBio Interaction Laboratory at Tehran University of Medical Sciences (http://www.biospion.com). He is recognized through his outstanding works in the area of "Overlooked Factors" at the (nano)biointerfaces. His current research involves control of protein corona decoration at the surface of nanoparticles and hidden parameters that affect the nanobio interfaces for efficient cardiac and neurological applications.

According to the National Aeronautics and Space Administration (NASA) report, the average temperature of the earth during 2013 was 14.6 °C (Celsius degree), which is 0.6 °C warmer than the mid-20th century baseline.[1] Till now, two major sources have been considered for this global warming: the first is natural warming is occurred periodically in different geological eras, as a result of volcanic eruptions, solar energy reaching the earth, etc.;[2,3] The second source mentions human activities as a cause of global warming.[4] About 150 years ago when human used fossil energies increasingly for industrial purposes, the process of global warming started becoming a crisis.[5] Burning fossils mainly in engines and factories accompanied with increasing human population have reduced the ozone layer in the atmosphere. In this case, more solar energy has reached the earth, evaporation of water from sea surfaces increased, greenhouse gases produced and global warming remarked.[6] Therefore, unfortunately, one can expect that there would be no "pause" in the global warming. Very recently, the new Clean Power Plan center has been founded in the US to remove the coal-fired power plants and fight against fast climate changes.

Although the amount of raised average temperature is below 1 °C, the evidence shows that it has considerable effects on the life of different kinds of organisms on the earth.[7] Defreezing natural polar glaciers, decreasing the length of cold seasons, and increasing warm months are just a few examples of the result of global warming.[8,9] Human health, like that of many other living organisms on the earth, could be affected by the consequences of the global warming.[10] Increasing the rate of different kinds of cancers including skin tumors (as a direct consequence)[11,12] and neurodegenerative disorders (as an indirect consequence) could be considered in this category.

For hundred millions of years the earth has coped with

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various types of climates. Ice age, global warming, dryness, and moisturizes eras are examples of climates that have shaped the earth and run the evolution through different kinds of organisms. Evolutionary studies have shown that speciation (especially birth of humans) occurred when the climate changed.[13] In addition to creating new species, climate has driven adaption processes such as evolving homotherms to face with climate changes.[14,15] Adaptation is mainly involved changes in structure and size of DNA, which could in turn result in changes in gene expression, creating new genes and evolving more adaptable organism which could survive in variable climate conditions.[16]

It seems that among all environmental forces, hot climate has the most stressful effects on organisms. In particular, some genes-encoded proteins termed heat shock proteins (HSPs) has been created from billion years ago to protect organisms from heat stress.[17] In more complicated organisms HSPs have multifunctional activities which may indirectly help in response to heat stress. These groups of proteins have different members that mainly act as molecular chaperones, bind to denatured (heat affected) proteins and subsequently result in protein refolding or preventing aggregation of unfolded and toxic proteins. One of the most important members of HSPs is HSP 70. This protein has a crucial role in folding of nascent chain peptides, translocation of proteins across membrane and protection of proteins from high temperature effects by interacting with exposed hydrophobic surface of them.[18] It has been reported that HSPs (mainly HSP 70) have a significant role in protection of neurons from aggregation of toxic misfold proteins. Their malfunctions or depletions may contribute partly in pathogenesis of neurodegenerative disorders.[19,20]

In the nervous system heat and cold conditions are sensed by receptors functioning as ion channels in somatosensory neurons.[18] Heat could have both neuroprotective and neurotoxic effects.[21,22] In this case, heat shock protein and their downstream molecules including HSP 16.1 and PMR-1 Ca^{2+} pump located in membrane of Golgi apparatus exert neuroprotective effect against heat death.[23] Interestingly, spatial learning occurs at brain temperature between 30–39 °C and various bioelectrical signals are more sensitive during warming that needs electrophysiological responses. Warming also speeds up axonal conduction, releases stimulus elicited transmitter, and increases rate of action potentials.[24] Moreover, heat shock below 39 °C might result in increasing IL 1beta and IL 6 expressions.[25] Although mild warming has some physiological effect on nervous system, increasing body temperature above 40 °C also called hyperthermia could have adverse effect.[26-28] Hyperthermia means increasing body temperature up to 40.6–41.7 °C. The event could result *from hot climate*, uncontrollable infection and genetic disorders.[29]

It is now well known that brain temperature during stroke is higher than the rest of the body which results in poor prognosis on disease treatment. This may have occurred because of increasing metabolic rate, limited amount of ATP and O_2 and increased amount of free radicals and toxic substances which might have occurred during stroke.[24,30] In this case, different lines of studies have shown that heat even at tolerable range for human body can induce apoptosis signaling pathways, worsened ATP depletion and cell volume shrinkage, endoplasmic reticulum (ER) stress and activating apoptotic signal transduction.[13,18] Temperature higher than the predetermined range may cause cell necrosis.[18] On the other hand, exposing ischemic patients to hypothermia could protect central neurons from degeneration.[31] Interestingly, temperature of 32 °C can protect cells from ER stress, DNA damage, Fas mediated apoptosis by P53 dependent and independent pathways.[13,31]

In related cases some studies have shown that hyperthermia could result in Alzheimer's disease (AD)-like molecular phenotype including increase in amyloid beta formation in animal studies, deposition of phosphorylated tau[32] and blood brain barrier dysfunction.[33] It is also demonstrated that slight changes in the temperature can considerably change the folding of amyloid beta (a building block of AD) and accelerate the fibrillation process.[34]

According to the predictions, the rising in average temperature of the earth will hit 4 °C, thus, the global warming may increase the risk factor for diverse types of diseases including neurodegenerative disease.[35,36] It is well agreed that the prevalence of neurodegenerative disorders have rapid increasing trend in different populations.

It was shown that the temperature variation effects on metabolism will be the greatest in the tropics compared to the Arctic area.[37] More specifically, it is well understood that the small temperature changes can push tropical organisms beyond their optimal body temperatures and, thus, may cause substantial stress; on the contrary, organisms in temperate regions have capability to tolerate much larger increases due to the fact that they are experienced at encountering large seasonal temperature swings.[37] Although humans are homothetmic organisms, the hot climate had profound effect on their health. Global warming results in increasing duration of hot seasons and studies have reported that hot weather could threaten human health and increase rate of death.[8] In addition, it was found that dementia-suffering people (e.g., AD) have considerable circadian dysfunction in their core body temperature (such dysfunction may preface the clinical onset, and the disease severity could correlate with the magnitude of circadian dysfunction)[38,39] and, thus, they would be more affected by the global warming phenomenon.

According to the discussed issues, we hypothesize that global warming can significantly increase the rate of neurodegenerative disorders by inducing persistent heat stress even at tolerable temperature ranges for neurons. The event may result in induction of apoptotic pathways, DNA damage and aggregation of heat affected proteins inside these cells, which could further expose susceptible neurons to degeneration. Thus, we ask neuroscience researchers to access the importance of issue. In particular, the effect of slight temperature changes on the function and activity

of the heat shock proteins and their consequent pathways should be precisely probed. In addition the correlation of the global warming map and prevalence of different types of neurodegenerative disorders at global level should be considered.

Ethical issues

There is none to be disclosed.

Competing interests

None to be declared.

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