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Cooling Core Body Temperature May Slow Down Neurodegeneration

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Faculty Affiliations and Disclosures

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Focus Points

- Reduction of core body temperature has been proposed to contribute to increased lifespan and the anti-aging effects conferred by caloric restriction in mice and higher primates.
- Having cooler biologically compatible core body temperatures may also combat neurodegenerative disorders.
- Engineered transgenic mice were shown by researchers to have lower core body temperatures and live longer independent of alteration in diet or caloric restriction.
- Discovery of new data is of significance for humans because there are many existing methods to lower and maintain low core body temperatures in human subjects.
- Employing physical fitness is perhaps the safest and best recognized way to lower core body temperatures.

Abstract

Reduction of core body temperature has been proposed to contribute to the increased lifespan and the anti-aging effects conferred by caloric restriction in mice and higher primates. Cooler biologically compatible core body temperatures have also been hypothesized to combat neurodegenerative disorders. Yet, validation of these hypotheses has been difficult until recently, when it demonstrated that transgenic mice engineered to have chronic low core body temperature have longer lifespan independent of alteration in diet or caloric restriction. This article reviews the literature and highlights the potential influence of core body temperature's governing role on aging and in the pathophysiology of neurodegenerative disorders in humans. What makes recent findings more significant for humans is the existence of several methods to lower and maintain low core body temperatures in human subjects. The therapeutic potential of "cooler people" may also raise the possibility that this could reverse the adverse-health consequences of elevations in core body temperature.

Introduction

Oxidative stress, oxygen-demand overload and inflammation have been identified as three principle mechanisms involved in or leading to cellular damage, which, in turn, provide the underlying causes for neurodegenerative diseases, aging, and a variety of other medical conditions.[1] All three mechanisms have been shown to be partially controlled and favorably influenced by cooler core body temperatures.[2]

The Arrhenius rate law (ARL)[3] mandates that all chemical reactions go faster with higher temperatures and that the relationship between temperature and the speed of the action is exponential. Consistent with the ARL, the preponderance of empirical evidence points to temperature attenuation as a powerful weapon by itself or as an adjunct to others in fighting a large class of ailments, including diseases such as Alzheimer's disease.[2]

Reduction of core body temperature has been proposed to contribute to the increased lifespan and the anti-aging effects conferred by caloric restriction in mice and higher primates.[4] The most robust intervention for slowing aging and maintaining health and function in animals is dietary caloric restriction.[4] Evidence suggests that caloric restriction lowers core body temperature in rodents, Rhesus monkeys, and humans.[4] Drop in core body temperature in humans is in the range of 0.5° to 1.0° C.[4] Because of the laws of thermodynamics expressed through the ARL, we have previously hypothesized and stated as Salerian-Saleri Thesis of Temperature[2] that cooler biologically compatible core body temperatures may combat neurodegenerative disorders and prolong longevity in humans.

Of particular importance is the narrow range of the temperature drop that is compatible with life. In essence, we had hypothesized that caloric restriction offers two pathways combating aging and neurodegenerative disorders: control an attenuation of concentration of key agents in biochemical reactions and lower temperature of the medium. Since temperature reduction is a consequence of caloric restriction, part of the associated benefits may be due to cooler temperature's slow-down effect on product streams as mandated by the ARL.

Physical Fitness Lowers Body Temperature and Increases Brain Volume in Humans

Core body temperature and specifically brain temperature play a key role in athletic performance. Steady training improves the body's ability to negotiate thermal stress and hence enhances its thermal stability.[5,6] Through exercise, training, and acclimatization, it is possible to improve the body's thermoregulatory response to thermal shock, while also lowering the core body temperature as reported by Baum and colleagues[5] and Koliass and colleagues.[6] These studies highlight the utility of physical fitness as a vehicle to achieve lower core body temperatures.

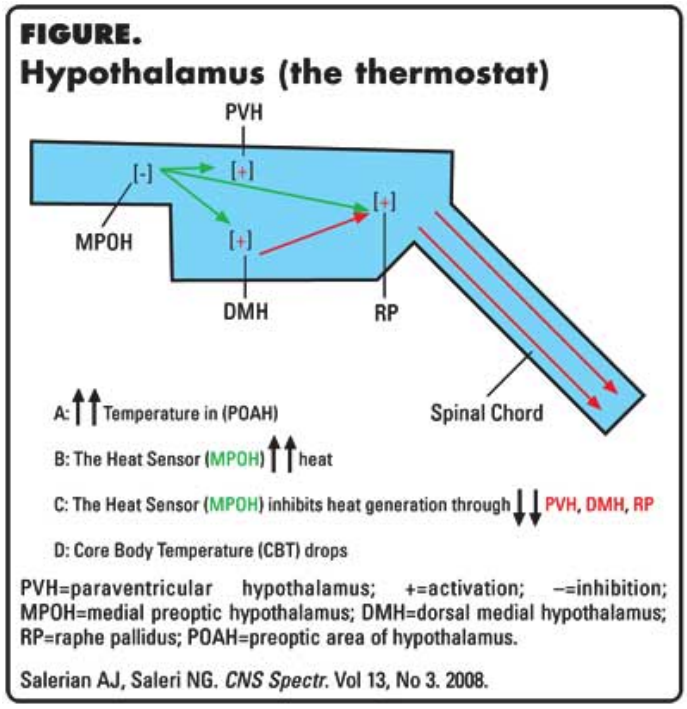
A recent study by Colcombe and colleagues[7] demonstrated that cardiovascular fitness is associated with the sparing of brain tissue in aging humans. Furthermore, they demonstrated that aerobic fitness can enhance central nervous system health and cognitive functioning in older adults. Significant increases in brain volume in gray and white matter regions on magnetic resonance imaging were found as a function of a 6-month fitness training for the older adults who participated in the aerobic fitness training, but not for the older adults who participated in the stretching and toning control group.[7]

Collectively, the results of Baum and colleagues[5] and Colcombe and colleagues[7] support the hypothesis that

cardiovascular fitness reduces core body temperature and enhances brain structure and function in humans, possibly slowing neurodegeneration.[2]

Transgenic Mice with Lower Body Temperature Longer Lifespan

Validation of Salerian-Saleri Thesis of Temperature has been difficult in homeotherms until recently, when Conti and colleagues[8] reported that transgenic mice engineered to overexpress the uncoupling protein-2 in hypocretin neurons have elevated hypothalamic temperature with a reduction of core body temperature by 0.3° to 0.5°C.[5] Conti and colleagues[8] highlight the influence of core body temperature on aging and neurodegeneration. They produced transgenic mice with lower core body temperature that were independent of diet or caloric restriction. These designer mice had tiny heaters in the preoptic area of the hypothalamus due to their uncoupling protein-2 gene, the gene that controls the promoter of hypocretins produced in the lateral hypothalamus. The researchers hypothesized that increased heat production within or proximate to the preoptic area mimicked a natural increase in core body temperature that resulted in feedback reduction in core body temperature (Figure).



The effect of elevated hypothalamic temperature on core body temperature was studied using radiotelemetry in male and female mice. The cool mice maintained a normal circadian variation of core body temperature and also showed unaltered thermogenic capacity by developing a fever response similar in amplitude and duration of the wild-type mice after injection with Escherichia coli lipopolysaccharides. The drop in core body temperature averaged 0.34° C in females and 0.3° C in males.

To investigate whether reduced core body temperature prolonged lifespan, Conti and colleagues[8] compared the survivorship of cool mice with wild-type littermates fed ad libitum on 11% fat (kilocalorie) diet. Despite their high caloric intake, the cool mice showed a 25% reduction in mortality rate across adulthood. In essence, They proved that a modest and prolonged reduction of core body temperature can contribute to increased median lifespan in mice in the absence of caloric restriction.

Conclusion

What makes Conti and colleagues'[8] findings more exciting are the reality that there are several known methods to cool

and maintain a slightly lower core body temperature in humans. For instance, it has been demonstrated through exercise, training and acclimatization that it is possible to improve the body's thermoregulatory response to thermal shock while also lowering the core body temperature.[5,6] In addition, there are medications, such as melatonin[9] and sodium oxybate,[10] with demonstrated hypothermic effects. Of concern, however, are the potential yet unknown adverse effects of chronic lowering of core body temperature compatible with life for humans. For instance, will chronic lower body temperatures compatible with life induce negative changes in mental function or cause neuropsychiatric abnormalities? Animal studies to address potential adverse effects associated with chronic lowering of core body temperature will be of crucial importance.

In view of the known rapid progressive degeneration associated with amyotrophic lateral sclerosis or the rapid growth of malignant tumors, these may be good candidates for rapidly testing the potential efficacy of lowering body temperature. The fact that there are some inferences to primitive man having a core body temperature of 36° C[11] and the observation that elite athletes and physically fit individuals have lower core body temperatures may suggest that chronic cooler core body temperatures compatible with life may prolong longevity.

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