Life, the Universe, and Body Temperature

Clifford B. Saper

Science **314**, 773 (2006);
DOI: 10.1126/science.1135375

The efficiency of diffusive shock acceleration increases rapidly with the ratio of the shock velocity to the initial sound speed, a quantity known as the Mach number. Although most of the energy of the cosmic structure formation is dissipated in the centers of galaxy clusters, the shock waves in the outskirts and especially the accretion shocks have much higher Mach numbers and therefore should be more efficient particle accelerators, as can be seen in the figure (*2*).

Electrons, which can be accelerated to energies of 10^4 to 10^5 times their rest mass, produce radio emission due to their gyromotion in intergalactic magnetic fields. Such radio emission in galaxy clusters has been observed since the 1970s (*3*) and named cluster radio relics. However, only recently has the association with cluster merger shock waves been recognized (*4*).

Bagchi *et al.* have found a pair of giant radio structures and propose that the double relic in galaxy Abell 3376 may be emission from the accretion shock of the cluster. This dual radio morphology may be caused by the stronger matter flow onto the cluster along an embedding galaxy filament. If this interpretation is correct, it would be a remarkable finding, because it would imply the presence of magnetic fields in the infalling gas, whereas magnetic fields have so far only been detected within galaxy clusters. Furthermore, we would have the first observational identification of an accretion shock wave. Accretion shock waves are very interesting because they may be the origin of the still-mysterious ultra-high-energy cosmic rays (*5*), which are protons with energies up to 10^{20} eV. The highest energy electrons from such shocks can scatter photons of the cosmic microwave background into gamma-ray bands and thereby contribute to the observed and still unresolved gamma-ray background (*6*, *7*). As a result, the radio relics in Abell 3376 mark locations to be monitored in the future for all kinds of high-energy radiation.

There is another plausible explanation for the double relics, however. In the late stage of a violent merger of similarly sized galaxy clusters, an outgoing pair of shock waves emerges. These shock waves steepen as they run into the more dilute gas of the cluster outskirts, similar to tsunami waves propagating into shallower water. A resulting pair of radio relics was indeed observed in a morphologically similar merging cluster, Abell 3667 (*8*), and well reproduced by numerical simulations (*9*). Possibly, the relics in Abell 3376 are also of this type.

In any case, it is exciting that the radio relics in Abell 3376 provide us with direct insight into the fluid dynamics of cosmic structure formation. This important and surprising observation gives a foretaste of the radio glow of the cosmic large-scale structure (*10*), which one hopes to discern with the next generation radio telescopes such as the Low Frequency Array [LOFAR (*11*)], the Long Wavelength Array [LWA (*12*)], and the Square Kilometre Array [SKA (*13*)].

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10.1126/science.1133949

BIOMEDICINE

Life, the Universe, and Body Temperature

A hypothermic life-style may lead to a longer life. How good are the prospects?

Clifford B. Saper

In his book *Life, the Universe, and Everything*, Douglas Adams describes an advanced civilization that asks a supercomputer to calculate an answer to the Ultimate Question of "life, the universe, and everything." After several million years of calculation, the computer answers: "42."

Enhanced online at www.sciencemag.org/cgi/content/full/314/5800/773

A similarly inscrutable constant that we face in everyday life is 37, the mean body temperature measured in degrees Celsius of humans and most other mammals. We tend to take this number for granted, as it is always in the same, narrow range, until, of course, we become ill with a fever. We then take medications, usually inhibitors of prostaglandin synthesis (aspirin, ibuprofen, etc.), which typically brings our body temperature back to normal. But why is 37°C "normal", and is this truly the optimal operating temperature for our bodies?

On page 825 of this issue, Conti *et al.* (*1*) question this dogma. Surprisingly, their results suggest that our usual body temperature may not be optimal, at least in determining our life span. Their work is based on a growing revolution in our understanding of how the brain controls body temperature. Although it has been known for decades that the preoptic area—the most rostral tip of the hypothalamus—is both thermosensitive and necessary for maintaining normal body temperature, the details of the neural circuits that control body temperature have only recently begun to be elucidated (*2*). It is now understood that neurons in the medial preoptic region have an intense inhibitory effect on thermogenic responses (see the figure). Other neurons in the middle part of the hypothalamus, including the paraventricular and dorsomedial nuclei, have an excitatory effect on thermogenesis, but are normally held in check by the preoptic neurons. The interplay between the thermogenic neurons and those in the medial preoptic nucleus that hold them in check is critical in controlling body temperature under a wide range of conditions. The hypothalamic sites, furthermore, have descending inputs to brainstem and spinal areas that control autonomic thermoregulatory responses. By shifting blood flow to cutaneous blood vessels, heat can be exhausted,

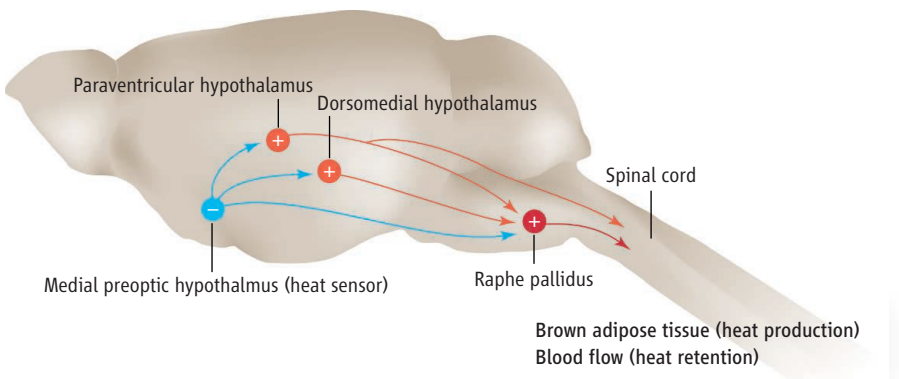
The author is in the Department of Neurology, Division of Sleep Medicine, and Program in Neuroscience, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA. E-mail: csaper@bidmc.harvard.edu

whereas heat retention is promoted by shifting blood flow to deep blood vessels (hence fingers and toes turn blue in the cold).

Thermogenesis is subserved by neural inputs to brown adipose tissue, at least in small mammals, where β_3 adrenergic receptors mediate production of uncoupling protein 1 (UCP-1). UCP-1 allows mitochondria in brown adipose tissue to convert adenosine 5′-triphosphate (ATP) to heat, rather than to energy for performing work. Thus, small mammals that lack sufficient mass for heat retention carry portable heaters in the form of brown adipose tissue that allow them to avoid hypothermia.

Here is where the intervention engineered by Conti *et al*. comes in. They produced transgenic mice in which expression of the UCP-2 gene (closely related to UCP-1) is placed under the control of the promoter for hypocretins (also called orexins). Hypocretins are peptides that are produced only by cells in the lateral hypothalamus (*3*). By placing UCP-2 expression under the control of this promoter, the investigators effectively placed a small heater into the hypothalamus. As their data show, this caused heating of the preoptic area, a region in which previous work had shown that insertion of heat probes would cause a reduction in body temperature. The result is that the transgenic animals expressing the UCP-2 gene had a continuous reduction in body temperature by 0.3° to 0.5°C.

Surprisingly, there has been little previous work on the effects of life-long hypothermia on other physiological functions in mammals, mainly because the brain normally maintains a constant body temperature so thoroughly that any change from this condition is rather difficult to achieve. In the Conti *et al*. experiments, the hypothermic transgenic mice showed no change in food intake or physical activity, but their body weight did increase, presumably due to a lower basal metabolic rate. One might expect, given the accumulated evidence that increased weight correlates with a variety of disorders that shorten life (*4*), that the hypothermic mice might have had a shorter life span. But in fact, the opposite was the case. Not only did the hypothermic animals live about 3 months longer than the 27-month mean life span for control mice, but they also had a parallel mortality rate, as if the mortality curve had been shifted to the right by about 10% of the life span. A corresponding percentage increase in human life span would be 7 to 8 years, a sizable change in longevity. If this were due to a delay in senescence, as the shift of the mortality curve in the hypothermic mice would suggest, rather than merely a prolongation of it, this could substantially increase lifetime productivity in humans.



Temperature control center. In the mammalian brain (mouse brain shown), a series of neural pathways (red) control the body's autonomic responses that regulate heat conservation and production, respectively. Cells in the paraventricular and dorsomedial hypothalamic nuclei, and in the raphe pallidus, signal to sympathetic preganglionic neurons in the spinal cord to control thermogenesis. These pathways are in turn regulated by an inhibitory input (blue) from the medial preoptic hypothalamus that is responsive to preoptic temperature.

Perhaps we should not be surprised by this result, because low body temperature does prolong life span in poikilothermic fish (in which body temperature fluctuates with that of the external environment) (*5*). Homeotherms with a restricted caloric intake develop a low body temperature and also have a prolonged life span (*6*). But few people would choose a life-style that limits their caloric intake, and Conti *et al*. provide the first test of the hypothesis that lowering the body temperature of a mammal prolongs life. The substantial increase of life span raises the question of whether mild hypothermia of 0.3° to 0.5°C might be easier to tolerate than a lifetime of starvation, as a way to increase longevity. Although at present there is no practical way for humans to achieve prolonged hypothermia, the results of Conti *et al*. suggest a potential gene therapy approach. One could imagine, for example, stereotaxic injections into the hypothalamus of an adeno-associated virus or lentivirus engineered to provide long-term expression of an uncoupling protein, to warm the hypothalamus just enough to extend life span.

If life-span extension could be this simple, one might wonder whether 37°C is indeed the optimal body temperature for humans, and why evolution has not selected for a lower body temperature and longer life span. However, there would be little evolutionary pressure to extend the number of years of life after reproduction is finished. A more important question for humans contemplating a hypothermic life-style might be whether the lower body temperature in the UCP-2 transgenic mice might cause other physiological or behavioral problems, such as changes in reproductive physiology, which might select against a lower body temperature. The reasons for the remarkable stability of body temperature among mammals, and why this temperature has been selected by evolution, remain obscure, although one would certainly want to know the consequences of hypothermia before pursuing it as a way to increase life span.

In Adams's book, the scientists ask the supercomputer how the answer to the Ultimate Question of "life, the universe, and everything" could be "42." The computer answers that to understand the answer, they have to know what the Ultimate Question is, and that it will take several million more years to determine that. We hope that we will not have to wait as long to understand why evolution has designed us with a body temperature of 37°C. The new and unexpected vista on the relation between body temperature and longevity opened up by the report of Conti *et al*. may help expedite the process. This work also holds out the tantalizing promise that we may be able to achieve a longer life span, if we were only to be a little cooler about it.

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10.1126/science.1135375

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