Hypothalamic control of body temperature: insights from the past

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This essay looks at the historical significance of three APS classic papers that are freely available online:


In the field of temperature regulation certain observations were critical in developing a clear understanding of how body temperature was regulated in homeotherms. The first important observation was the thermosensitivity of the hypothalamic region. Early work by Barbour (1) and Ranson et al. (7) showed that heating the brain near the preoptic hypothalamic (POAH) region caused cutaneous vasodilation and panting. In 1961 Nakayama et al. (6) discovered thermosensitive neurons in the hypothalamus. These observations caused many neurophysiologists interested in thermoregulation to focus their attention on the analysis of thermosensitive neurons in the POAH area. A second important observation was the description of signal processing within the POAH for the regulation of body temperature based upon a proportional controller with an adjustable set point. This description, by Ted Hammel and colleagues (4) at the John B. Pierce Laboratory in 1963, directed the evolution of our understanding of thermoregulatory control. The following paragraphs provide some insight into how Ted Hammel (Fig. 1) developed his model of hypothalamic control of body temperature.

It was an unlikely place to meet, but it was in the mess hall of the Artic Aero Medical Laboratory at Ladd Field Air Force Base in Fairbanks, Alaska, that the young graduate student from Cornell University, Ted Hammel, ate meals and discussed research with James D. Hardy and Alice Stoll. While the outside temperature dipped to −20°C, the discussions remained heated and exciting. By the time Hardy left Fairbanks, he was so impressed with the young Mr. Hammel that he offered him a position in his laboratory to continue research in the field of temperature regulation. In September 1953, Ted moved his family to Media, Pennsylvania, and began his work with Dr. Hardy at the University of Pennsylvania School of Medicine. Using a multichannel recording potentiometer, Ted would spend hours viewing the millivolt outputs from the gradient layer calorimeter, oxygen analyzer, humidity analyzer, and thermocouples measuring body core (rectal) temperature and seven skin temperatures. Ted noted that “I would often watch the recorder printing out this data and try to anticipate from skin and rectal temperatures when the conscious, resting, awake dog would shiver in a cold environment or pant in a hot environment. I could never predict the onset of shivering or panting.”

Based on research with humans in the Russel Sage calorimeter at Cornell, Dr. Hardy proposed that the thermal drive for these thermal regulatory responses was 1/4 core and 3/4 average skin temperature where each skin thermocouple output was weighted in proportion to the area of the body surface represented by that thermocouple. However, this hypothesis puzzled Ted because he was unable to repeatedly predict the thermal regulatory responses caused by skin and core temperatures in

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Fig. 1. H. T. Hammel.
conscious dogs. There had to be a better way to explain how core and surface temperatures are utilized by the central nervous system to elicit the appropriate responses to cold and hot environments.

At the time, it was known that the hypothalamus was strongly implicated in the regulation of body temperature. So, around 1957 Ted decided to implant thin-walled stainless steel tubes, sealed at their lower ends, next to the POAH nuclei. He called these tubes “thermodes” as opposed to “electrodes.” He constructed a small double-chamber system that allowed him to heat or cool the POAH nuclei at will and to any degree of temperature he chose, while the dog was enclosed in a calorigram. By this means, he was able to open the feedback loop around 1957 Ted decided to implant thin-walled stainless steel tubes, sealed at their lower ends, next to the POAH nuclei. He called these tubes “thermodes” as opposed to “electrodes.” He constructed a small double-chamber system that allowed him to heat or cool the POAH nuclei at will and to any degree of temperature he chose, while the dog was enclosed in a calorigram. By this means, he was able to open the feedback loop involved in the regulation of body temperature. In 1960 Ted presented these findings (3) at the International Union of the Physiological Sciences meeting held in Buenos Aires. His roommate at the meeting was Theodor Benzinger. Ted recalls that when he told Dr. Benzinger that he was able to cool the POAH nuclei of conscious dogs in a hot environment and cause them to shiver “he did not believe me.” At the time, Benzinger’s vision of the “human thermostat” did not allow the temperature of the hypothalamus to elicit shivering. He believed that a high hypothalamic temperature could only lessen shivering already elicited by cold receptors in the skin activated by cold exposure. But a low hypothalamic temperature alone could not elicit shivering.

In 1961 Ted followed Dr. Hardy to the John B. Pierce Laboratory and Yale University and continued to heat and cool the POAH nuclei of dogs. It was clear to Ted that shivering could be elicited by cooling the POAH nuclei and panting could be elicited by heating the POAH nuclei. Furthermore, the threshold hypothalamic temperatures for shivering and panting increased in the cold environment, and these threshold temperatures decreased in the hot environment. With this information and more, he published the article titled “Temperature regulation by hypothalamic proportional control with an adjustable set point” in the Journal of Applied Physiology (4). The title of the manuscript told the story. The original manuscript had a figure that depicted how Ted imagined neurons in the POAH might be related so as to yield the results he reported. Loren Carlson was Editor for the Environmental Physiology Section of the Journal of Applied Physiology at the time and thought it would not be appropriate to speculate to this extent, so the figure was left out. It took Ted two years to get the figure published in a chapter titled “Neurons and Temperature Regulation” in Physiological Controls and Regulations, edited by W. S. Yamamoto and J. R. Brobeck (2).

Ted published a series of papers using this awake dog model. Bjorn Hellstrom spent a year in his laboratory and measured the temperature of the POAH when resting dogs were exposed to ambient temperatures from 10°C to 40°C. The POAH temperature fluctuated a few tenths of a degree centigrade at each ambient temperature, but the fluctuations at 10°C could not be distinguished from the fluctuations at 40°C (5).

Because of these observations Ted wondered if “the POAH nuclei were needlessly sensitive to temperature?” However, Ted and Bjorn had missed something. When they later plotted evaporative heat loss via panting in the dog as a function of POAH temperature, the relationship was good enough to demonstrate some characteristics of the POAH regulator. Their new analysis indicated that the threshold hypothalamic temperature for panting increased with decreasing skin and core temperatures. Second, the slope of the response curve (the gain of the regulator) also increased with decreasing skin and core temperatures. Ted used this information to modify his neuronal model. The model depicted the firing rates of the temperature-insensitive neurons being facilitated by cold receptors from the skin and core. The neurons for activating panting were depicted as activated when facilitation from the temperature-sensitive neurons exceeded inhibition from the temperature-insensitive neurons. Thus, this could explain why placing the dog in a cold environment facilitated the temperature-insensitive neurons and these, in turn, increased inhibition of the “panting” neurons.

Ted continues to be active today and can usually be found wandering around the annual American Physiological Society meeting. His thoughts on this topic are as fresh and exciting today as they were in 1963. Ted’s contributions and insights into the field of temperature regulation should remind latter-day scientists of the remarkable work of their forebears and its relevance to the research today.

REFERENCES