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Introduction to temperature regulation

Temperature regulation (or thermoregulation) can be defined as the control of the temperature(s) of a body under finite environmental conditions. Regulation is achieved by controlling heat gain and heat loss between the body and the environment through the utilization of autonomic and behavioral mechanisms. Birds and mammals have evolved a battery of behavioral and autonomic motor outputs (i.e., effectors) to regulate their core body temperatures within narrow limits when subjected to a wide range of ambient temperatures (Prosser and Heath, 1991). In some cases, reptiles, fish, and amphibians are able to regulate their body temperatures by means of behavioral responses. Invertebrates are *temperature conformers,* meaning that their body temperatures usually are about the same as that of their surrounding environment. Even the most primitive organisms display thermotropism (i.e., the tendency to turn toward or away from a heat source), and many temperature conformers have distinct behavioral thermoregulatory responses (Whittow, 1970; Prosser, 1973). It should be remembered that ambient temperature is probably the most critical environmental factor in limiting an organism's choices among possible habitats. Thus the development of temperature regulation undoubtedly has played a major role in evolution.

1.1. A brief historical perspective

The existence of thermoregulatory systems probably was one of the earliest discoveries of an involuntary homeostatic process, as reviewed by Lomax (1979), Folk (1974), and Hensel (1981). That is, before recorded history humans surely must have recognized that many diseases were associated with a feeling of warmth on the skin, whereas death brought on a loss of heat. The ancient Greek philosophers conceived a relationship between body heat and

the vitality of living organisms. They believed that the left ventricle was the source of one's innate heat, and respiration was a vital process needed to cool the body.

Basic empirical observations mixed with religious dogma were used to explain thermoregulatory phenomena in humans until late in the seventeenth century. It was not until the late eighteenth century that modern theories of thermoregulation began to take shape. Lavoisier made some of the first measurements of heat loss in a rat, using a crude, albeit accurate, ice-bath calorimeter. In the early 1800s, measurements of body temperature and cold resistance in various species of mammals and birds were undertaken.

The development of the clinical thermometer by Allbutt in 1867 spurred research on fever and other thermoregulatory processes. Indeed, recognition of the existence of fever was perhaps the most critical factor in galvanizing research into the mechanisms of temperature regulation. During the latter 1800s it was realized by Libermeister and others that fever was not the cause of disease, but rather was a regulated elevation in core temperature and a symptom of disease.

By the early 1900s, as a result of the pioneering work of Rubner and others using direct calorimeters, a substantial data base on body temperatures and metabolism among numerous species had been developed. Detailed monographs on the temperature regulation of the laboratory rat had been published by the 1930s (e.g., Benedict and MacLeod, 1929). One of the most exciting areas of investigation into temperature regulation during the first half of the twentieth century was the search for the central nervous system (CNS) loci involved in the control of body temperature. Researchers such as Bazett, Ranson, and Magoun in the 1930s were instrumental in developing the concept of the anterior/posterior hypothalamus as the key regulatory site for control of body temperature. Spurred by military interests, research in the 1940s and 1950s focused on understanding the limits of thermoregulation in humans and other species when exposed to severely warm and cold environments. Also during that time, considerable progress was made in measuring thermal homeostatic processes in reptiles and other lower vertebrate species (e.g., Cowles and Bogert, 1944).

The work by Irving and Scholander was particularly noteworthy in describing the relationship between a species' thermoneutral profile and its adaptability to cold environments (e.g., Scholander et al., 1950). Soon after that, a multitude of studies on the thermoregulatory characteristics of wild and domesticated rodent species were carried out by J. S. Hart, F. Depocas, and many others (e.g., Hart, 1971). In the 1960s, the utilization of stereotaxically implanted thermodes to heat and cool the brain stem in awake

animals (e.g., Hammel, 1968; Heath, Williams, and Mills, 1971), the first recordings of hypothalamic temperature-sensitive neurons by Nakayama (Boulant and Dean, 1986), and the discovery that body temperature could be manipulated by CNS injections of neurotransmitters (Feldberg and Myers, 1964) elevated thermoregulatory research in experimental animals and humans to a new level of understanding. Another key advancement in the field was the development of a concise glossary of thermal physiology, first prepared by Bligh and Johnson in 1973. That glossary was later expanded and refined by the International Union of Physiological Sciences (IUPS, 1987).

1.2. Current research status of thermoregulation

The past status and current status of thermoregulatory research in mammals pose somewhat of a paradox. On the one hand, as can be seen from the foregoing discussion, thermoregulatory research has played a key role in the development of our modern concepts of physiology. Yet, of the thousands of researchers in the life sciences and related fields, only a relative handful currently dedicate their primary research to thermoregulation, totaling approximately 300 worldwide (Refinetti, 1990a).

A variety of reasons can be cited for the waning interest in basic thermoregulatory research. In my opinion, a chief factor is that because the thermoregulatory system works so well, it has never been seen as a prime area in need of research funding. That is, thermal homeostasis in humans and other mammals is maintained 24 hr per day from soon after birth until death, with relatively little aberration. Congenital defects in thermoregulation in humans are extremely rare. Moreover, under most environmental conditions (i.e., barring extreme thermal stress, drug overdose, severe trauma, etc.), thermoregulatory systems rarely experience sudden failure or show ''life-threatening'' deficits. On the other hand, dysfunctions of other regulatory systems of key interest in the biomedical community, such as the cardiovascular, renal, hepatic, gastrointestinal, and immune systems, are the major causes of human disease and mortality. Indeed, often medications must be prescribed for much of person's lifetime to prevent malfunction or failure of the heart, kidney, liver, CNS, or other systems. But thermoregulation generally operates with few flaws until one is near the point of death, and therefore it has not been a major focus in the funding decisions in biomedical and related research in recent times.

After reading the foregoing, one might view the future of thermoregulatory research with pessimism. There are, nonetheless, several reasons that research in this field is essential:

1. That the thermoregulatory system works so well clearly makes it an excellent paradigm of biological regulation. The system achieves a fine degree of control by utilizing the functions of other organ systems for its motor outputs: the respiratory and digestive systems (e.g., salivary glands in rodents) for evaporation, the cardiovascular system for skin temperature, and skeletal muscle for shivering and behavioral thermoregulatory responses. Only brown adipose tissue appears to have evolved solely for a thermoregulatory function. Surely, if one could fully understand the workings of a multiorgan regulatory system that rarely fails, then a better understanding of other, more vulnerable autonomic systems should be forthcoming.

   Of course, the thermoregulatory system is not flawless. Like other bodily functions, thermoregulation is most susceptible to dysfunction during the early and late stages of life. The very young and the elderly are more likely to encounter thermoregulation-related maladies such as hypothermia and hyperthermia. Certain pharmaceutical therapies, toxic chemicals, stress, and other environmental and biological agents can reduce the normal ambient temperature range of thermoregulation and thereby increase its susceptibility to dysfunction.
2. Like the output from other autonomic systems, the output of the thermoregulatory system affects the functioning of all other physiological processes. That is, mammalian enzymes have evolved in a relatively stable thermal environment of 37°C and have narrow temperature ranges for optimal functioning. Thus, deviations from normal body temperatures will lead to significant changes in enzymatic activity and, hence, the functioning of a given physiological system. This becomes especially pertinent in rodents, which have more labile thermoregulatory systems than do larger species (see Chapter 9).
3. The thermoregulatory system is unique among the homeostatic processes from the standpoint that it relies on higher-level CNS processes for thermal detection and elicitation of corrective behavioral motor responses. Behavioral sensation of skin temperature is an incredibly sensitive and continuous process. It is of paramount importance in the activation of autonomic and behavioral motor outputs. Yet, in the absence of behavioral responses, such as during sleep and certain forms of anesthesia, thermoregulation is still operative. On the other hand, behavioral input–output processes are not as pivotal in other autonomic processes, such as the regulation of blood pressure and of electrolyte and water balances.

The behavioral sensitivity of thermoregulation can be exemplified by a simple examination of human energy usage. Although autonomic motor outputs can achieve a regulated core temperature over a relatively wide range of ambient temperatures, our behavioral thermoregulatory processes cause us to expend billions of kilowatt-hours (and dollars!) in heating and air conditioning to keep our environment at a comfortable temperature of 22–26°C (72–78°F).

Behavioral thermoregulation is also critical in the thermoregulation of rodents (see Chapter 4). Behavioral responses are severely compromised when restraint is used, and totally abolished with anesthesia. Although these procedures are common to many experimental designs, their use in studying thermoregulation will eliminate a significant facet of the animal's motor outputs.

4. The process of fever, which involves a unique integration of the immune and thermoregulatory systems, continues to be a critical aspect of biomedical research. There still is considerable debate over the role of an elevated body temperature during fever and whether or not it is beneficial to recovery from infection. Elucidating the mechanisms of fever will continue to be a major endeavor in thermal physiology.
5. Manipulating the output of the thermoregulatory system (e.g., raising or lowering the core temperature) has been and will continue to be a crucial aspect of various surgical and therapeutic procedures. For example, without the advantage of hypothermia to lower the body's oxygen demand, it would be impossible to perform many of today's common surgical procedures on the heart and brain. Forced elevations and reductions in body temperature have proved to be extremely beneficial in treating some maladies, including some types of cancer and trauma to the CNS. Moreover, the efficacy and toxicity of drugs and other chemical agents can be markedly altered by changes in body temperature. This point is extremely important in rodent studies, because their body temperatures can change relatively quickly when subjected to a variety of stresses and trauma (see Chapter 9).

1.3. Why study laboratory rodents?

On the basis of these five points one can infer that there are two main avenues of thermoregulatory research: (1) studies on basic thermoregulatory mechanisms, including neural physiology, comparative differences, and ecological relationships, and (2) multidisciplinary research, in which the activity of the

thermoregulatory system may affect the functioning of another system that is the primary interest of the investigator. From this concern, a question arises: Which species is most appropriate for a given line of research in pure thermoregulatory research and/or a related response? The answer will depend on many factors, such as a species' thermoregulatory qualities per se, as well as its nutritional, cardiovascular, neural, immunological, and other characteristics that may be pertinent to one's specific line of research. At this point, a quotation from the eminent comparative physiologist C. Ladd Prosser is appropriate:

> Comparative physiology differs from other kinds of physiology in that the comparative approach uses the kind of organism as an experimental variable, and it emphasizes the long evolutionary history to life in diverse environments. [*Annu. Rev. Physiol.*, 48:1–6, 1986]

In other words, in the selection of a particular species of rodent or other organism for study, the researcher should be cognizant of its unique characteristics. Such knowledge can be invaluable for understanding the mechanisms of operation of a physiological system. This book strives to present these unique characteristics of the thermoregulatory systems of laboratory rodents in the hope of facilitating the comparative approach.

It is interesting to note that the amount of thermoregulatory research with rats and mice has increased considerably since around 1980 (Figure 1.1). The numbers of studies with hamsters and guinea pigs have been relatively constant since 1970, whereas work with gerbils has contributed a relatively small portion to the total rodent research effort. Research in nonrodent species, including cats, dogs, rabbits, and nonhuman primates, has shown a downward trend (Figure 1.1). There are perhaps several reasons for these patterns in animal research. The foremost factor obviously is the soaring cost of such research, which has led many to work with the less expensive laboratory rodents. Moreover, continuing pressure from various antivivisection groups has unfortunately caused many researchers to abandon their work with species such as cat, dog, rabbit, and monkey in favor of rodents.

1.4. Overview of temperature regulation in rodents

1.4.1. Terminology

The studies of temperature regulation can be broadly divided into two groups, dealing with species that are *tachymetabolic* and those that are *bradymetabolic*. Tachymetabolic species, which include birds and mammals, have relatively high basal metabolic rates compared with bradymetabolic species,

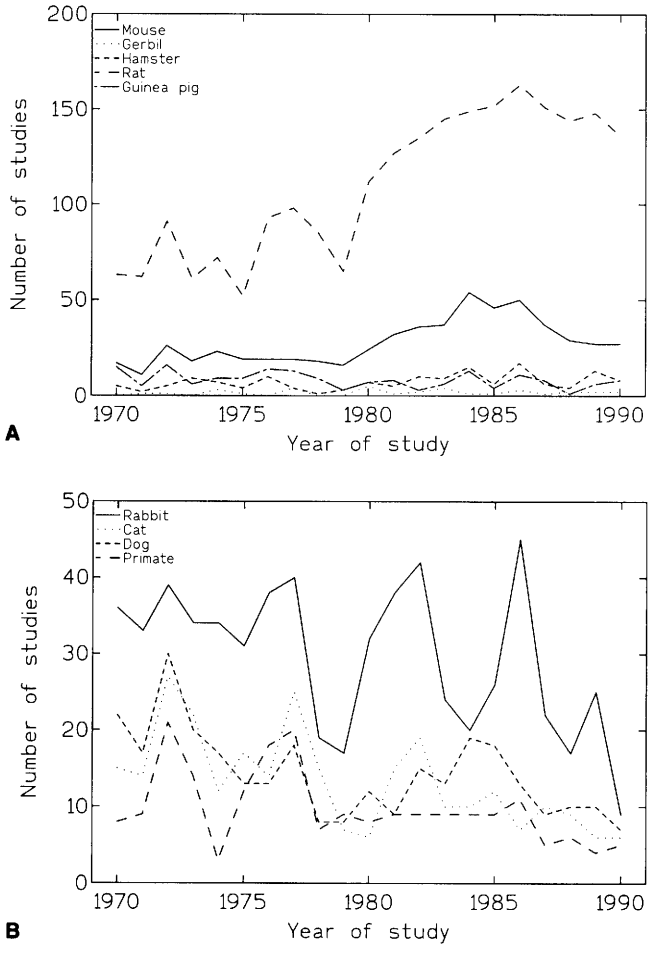

Figure 1.1. Frequency of publication of papers between 1970 and 1990 dealing with temperature regulation in key rodent (A) and nonrodent (B) species. These data were collected using a Medline literature search. Because of the restricted number of journals and possible ambiguity in the original indexing of titles, these graphs are likely to underestimate the actual numbers of studies.

including reptiles, amphibians, fish, and other species. Tachymetabolic species are also *endothermic*, meaning that their control of body temperature is dependent primarily on the generation of heat through metabolic processes. On the other hand, bradymetabolic species are *ectothermic*, meaning that their regulation is achieved behaviorally by controlling the transfer of heat between their bodies and their environment.

As with any scientific discipline, the terminology of temperature regulation can sometimes be ambiguous, depending on the species and the environmental circumstances (IUPS, 1987). For example, an endothermic species is almost always classified as a homeotherm, meaning that it can regulate its core temperature within relatively narrow limits (ca. ± 2°C). Yet many endotherms are not always homeothermic. Some birds and small mammals undergo diurnal or nocturnal torpor or annual periods of hibernation, allowing their core temperatures to drop markedly below the normal limits of homeothermy. In these instances the term *heterothermy* is used, wherein tachymetabolic species show marked daily or annual changes in core temperature.

Likewise, ectotherms are generally poikilothermic, meaning that in the absence of behavioral adjustments the animal's core temperature is closely dependent on the ambient temperature. However, many ectotherms, especially reptiles, use behavior to regulate body temperature within relatively narrow limits and thus display homeothermic characteristics. Also, some species of insects and fish, though classified as bradymetabolic, are nonetheless capable of endothermy and can actively increase their internal temperatures well above ambient levels (Prosser, 1973; Schmidt-Nielson, 1975b).

To summarize, the rodents are all tachymetabolic and rely on endothermy to regulate their core temperatures within relatively narrow limits. Among the laboratory rodents to be discussed in this book, the rat (*Rattus norvegicus*) and guinea pig (*Cavia porcellus*) are continuously homeothermic and are incapable of lowering their body temperatures under most environmental circumstances. The mouse (*Mus musculus*) is also homeothermic most of the time, but is capable of undergoing torpor during periods of food deprivation and thus can be classified as a heterotherm. The golden or Syrian hamster (*Mesocricetus auratus*) is also heterothermic at times and is capable of hibernating under proper environmental circumstances. The Mongolian gerbil (*Meriones unguiculatus*) is homeothermic most of the time but is apparently capable of torpor. It should be noted that this species has not been as well studied as other rodents.

1.4.2. Heat balance

The body's heat-balance equation is an appropriate place to begin a discussion of the fundamentals of temperature regulation in rodents and other species. It is a mathematical expression derived from the first law of thermodynamics, and it relates metabolic rate, work, and the four avenues for heat exchange to a species' bodily heat balance (IUPS, 1987):

$$S = M - W - E - C - K - R \tag{1.1}$$

where S is heat storage in the body (positive for an increase), M is metabolic rate, W is work (positive for mechanical work transferred to the environment, negative when mechanical energy is transferred from the environment to the body and is eventually converted to heat), E is evaporative heat transfer, C is convective heat transfer, K is conductive heat transfer, and R is radiative heat transfer. Each avenue of heat transfer is positive when there is a net loss of heat from the subject to the environment, and negative with heat gain. All variables in equation (1.1) are generally in standard energy units: watts (W), watts per square meter (W m^{-2}), or watts per kilogram (W kg^{-1}).

The avenues of heat exchange are factors of greater or lesser importance depending on the species and the environmental conditions. The rate of conductive heat transfer usually is quite low because so little of the animal's bare surface comes in direct contact with the substrate, but the rate of conductive heat transfer can become very high during water immersion. The rate of evaporative heat transfer is quite low under standard, room-temperature conditions (ca. 20–22°C), accounting for approximately 20% of total heat loss. Evaporative heat transfer increases markedly as ambient temperature is elevated above thermoneutrality (see Chapter 4). Thus, most of an animal's metabolic heat is dissipated by way of radiation and convection. Convective heat transfer increases in proportion to wind velocity, but air movement is generally quite minimal in most laboratory situations. Unfortunately, relatively little work has been done in laboratory rodents to measure the partitioning of heat exchange through the four major avenues, as compared with the number of studies in humans and other large species (e.g., Monteith and Mount, 1974).

Heat storage usually is expressed in terms of the rate of change in stored heat in the body and can be calculated as

$$S\ (\mathrm{W}) = \frac{c(\overline{T}_{b_1} - \overline{T}_{b_2})\ \text{body weight (g)}}{\text{time}_2 - \text{time}_1\ (\text{sec})} \tag{1.2}$$

where c is the specific heat of the tissues (~3.47 J g^{-1} °C^{-1}), and $\overline{T}_{b1}$ and $\overline{T}_{b2}$ are the mean body temperatures at the beginning and end of the time period. Thus, under conditions where heat production is equal to the sum of all avenues of heat loss, S is equal to zero, and the animal is normothermic (synonyms: cenothermic or euthermic); see IUPS (1987). When heat production exceeds heat loss, such as during exercise or following administration of a drug that stimulates cellular metabolism, S is positive, and the animal is hyperthermic. On the other hand, when heat loss exceeds heat production, such as during acute cold exposure or following administration of a drug that induces peripheral vasodilation, S is negative, and the animal is hypothermic.

When body temperature is constant (i.e., $S = 0$) and no work is being done, an endotherm's metabolic rate (M, in watts) must therefore match its total rate of heat loss (H_t) to the environment:

$$H_t = M = R + K + C + E \tag{1.3}$$

Incorporating specific terms for each of the avenues of heat loss, the metabolic rate is then calculated as

$$M = \epsilon\sigma A_r(T_b^4 - T_a^4) + h_k A_k(T_b - T_a) + h_c A_c(T_b - T_a) + \lambda\text{EWL} \tag{1.4}$$

where ϵ is the emissivity, or the ratio of radiant energy emitted by a body to the energy emitted by a full radiator at the same temperature (the value of ϵ is generally assumed to be 1.0 for animals, σ is the Stefan-Boltzmann constant (5.67×10^{-8} W m^{-2} °K^{-4}), A_r is the effective surface area for radiative heat exchange, h_k is the thermal-conductivity coefficient, A_k is the effective surface area for conductive heat exchange, h_c is the convective heat-exchange coefficient, A_c is the effective surface area for convective heat exchange, λ is the latent heat of vaporization (e.g., 2,411.3 J g^{-1} at 34°C), and EWL is the rate of evaporation of water. T_b is body temperature, but most appropriately would be the surface temperature of the skin or fur, and T_a is ambient or air temperature. (Note: For the radiative terms, T_a and T_b are in degrees Kelvin.)

There are several precautions to be considered when applying equation (1.4) to rodent thermal physiological studies. T_a is assumed to equal air temperature only when the temperature of the substrate (e.g., the floor) is equal to that of the air. Because the rate of conductive heat transfer normally is quite low, the differential of heat loss between the substrate and air usually can be ignored. Surface temperature is also very difficult to measure in rodents; thus, internal or core temperature is substituted for this variable. For temperature differences of 20°C or less, the Stefan-Boltzmann principle of radiant heat exchange can be disregarded, and a linear relationship for radiant heat loss can be assumed. Moreover, it is also quite difficult, if not impossible, to simultaneously measure A_r, A_k, A_c, h_k, and h_c. But thermal physiologists working with rodents have found that equation (1.4) can be further simplified to

$$M = C'(T_b - T_a) + \lambda\text{EWL} \tag{1.5}$$

where C' is whole-body thermal conductance and is approximately equal to $4\epsilon\sigma A_r T_a^3 + h_k A_k + h_c A_c$ (McNab, 1980). Clearly, thermal conductance is an extreme simplification of all the complex avenues of dry heat loss, but it is indeed a useful parameter for rodent thermophysiological studies (see Chapter 3 for further discussion). More detailed discussions of heat transfer