Mammalian Thermoregulation: Species Differences

N. R. BREWER, DVM, PHD,[1] AND LEON J. CRUISE, DVM, PHD[2]

Abstract | An understanding of the variation between species is a basic requirement if one is to give proper care to laboratory animals, select an appropriate animal to find answers to a specific question, and/or appreciate the limits in interpreting experimental results as they may apply to humans.

Introduction

Thermoregulation is an important variable. There are important differences because of size. There are important differences in tissue factors that affect thermoregulation. Among these are brown adipose tissue, leptin content, sweating ability, ability to pant, neural control, and heat shock proteins.

The optimum care of laboratory animals requires knowledge of physiology and physiologic differences between animals. For example, animals' production of heat and vapor, which vary among species, is often critical in the design of rooms housing them. Thermoregulatory differences may influence which biomedical model is chosen for a particular type of study.

All of the energy-requiring activities in the body (metabolism) eventually appear as heat, maintaining the body temperature (T_b) of euthermic mammals within narrow limits (1). The rate at which this heat is produced, the metabolic rate (MR), varies from a low (the basic metabolic rate [BMR]) when the body is at complete rest, in a thermoneutral environment, and in a postprandial state to a much higher level, which occurs during heavy muscular exercise.

The T_b can be divided into a "core" temperature and a "shell" temperature (8). The core comprises the brain and the contents of the thorax and abdomen. The shell includes the skin and subcutaneous tissue, muscle, and limbs.

The thermoneutrality zone is the ambient temperature (T_A) at which maintenance of T_b is least difficult. When T_A is lower than the zone of thermoneutrality, the lower critical T_A (T_{cr}), additional heat must be generated to maintain the T_b. When the T_A is higher than the upper T_{cr} heat dissipation must increase (2). The upper and lower T_{cr} show species-specific variations. For example, the lower T_{cr} is 22°C in the Japanese monkey (*Macaque fuscata*; 3), 25°C in the rock hyrax (*Heterohyrax brucei*; 4), 30°C in the gerbil (*Meriones unguilculatus*; 5), 20°C in the chinchilla (*Chinchilla lanigera*; 6), and varies between 22°C and 32°C in the naked mole rat (*Heterocephalus glaber*; 7). Because measuring the BMR in animals is difficult (primarily because of digestive activities), the resting metabolic rate (RMR), a metabolic rate that ignores digestive activity, is assessed when animals are at rest in a thermoneutral environment (2).

Oxidation of 1 g carbohydrate requires 0.84 L O_2, whereas oxidizing 1 g fat consumes 2.0 L O_2, and oxidation of 1 g amino acid to its excretion product (urea or uric acid) takes 0.96 L O_2. The thermal equivalent of 1 L O_2 is 5.0 kcal (20.7 kJ) for the oxidation of carbohydrate, 4.7 kcal for fat, and about 4.5 kcal for amino acid. In the typical mammalian diet, the thermal equivalent of 1 L O_2 is about 4.8 kcal (20.1 kJ; 8). Changes in T_b affect the rate of O_2 consumption, the rates at which chemical bonds are formed or broken, the structure of proteins, the fluidity of lipids, electrostatic reactions, and the pH (1). Each increase of 1°C in T_b is accompanied by a decrease of about 0.019 pH units in the blood and cytosol (9). A reduction in pH decreases the charge on lipid-bound phosphates and reduces lipid fluidity (10). Other T_b-induced changes are discussed in the section under torpor.

Heat Generation

Large mammals generate more heat than do small mammals, but the amount of heat produced per unit weight declines with increasing weight. The basic rate among eutherian mammals is about 70 kcal $kg^{0.75}$ daily (8); in other words, for every doubling of the body mass, the basal metabolic rate per unit of body tissue decreases by about 15%. A 3.5 g shrew (*Sorex cinereus*) requires about 100 times more O_2 per g of tissue than does a 4000 kg elephant (*Elaphus maximus*). A room housing 100 kg of 25 g mice requires 60 times more O_2 hourly than does a room housing 100 kg of 12.5 kg dogs. Compared to the cells of large mammals, those of small mammals have more mitochondria (9), more double bonds in the fatty acids (10), and increased Na^+-K^+ pump activity across the cell membranes (11, 12). Further, the potassium uptake rate, an accurate measure of the activity of the Na^+-K^+ pump, is greater in small mammals (13).

The MR increases with activity, and small mammals cannot increase their MR as much as do large mammals. A mouse can only increase its RMR by a factor of 3 to 5, whereas a rat can increase this measure by a factor of 5 to 7, and humans can increase their RMR by 15 to 20 times. Generally, the larger the mammal, the lower the maximum rate of O_2 utilization (O_2) per kg of body weight. The Thoroughbred horse is an exception to this trend; this animal's maximum O_2 per kg body weight is 2 to 4 times that of the average human (14).

When T_A falls below the thermoneutrality zone, endotherms generate heat by shivering or exercise. Shivering is a form of muscular activity that serves only to produce heat. Many endotherms can produce heat by nonshivering thermogenesis (NST), a process mediated primarily by the action of norepinephrine on brown adipose tissue (BAT; 15). In contrast to white fat, BAT has extensive vascularization, many mitochondria, and proteins that uncouple the mitochondria from their ATP-generating activity so that the energy of oxidation is liberated as heat (16). BAT is found in all hibernating mammals as well as in many neonatal mammals, including humans. Two forms of BAT have been described (17). One form is expressed throughout the life of hibernators. The other form, a convertible form, participates as thermogenic tissue only during the early postnatal period; the convertible form is found in larger mammals (17). In cats, rabbits, and sheep, the conversion from the thermogenic form to the lipid storage form occurs during the first postnatal month. In humans, this conversion takes 15 to 20 years (18).

The neonate of the harp seal (*Pagophilus groelandicus*), a seal that breeds on drifting ice in the arctic seas in February and March, provides an extreme example of the amount of heat that can be generated from BAT (19). Because subcutaneous fat is a postnatal development, the pups are born with no insulation,

University of Chicago (ret.), 10800 Tara Rd., Potomac, MD, 20854; [2]Howard University, Veterinary Services - College of Medicine, Washington, D. C., 20059

and the wet infantile fur has no insulating value. Yet the pups do not shiver in the arctic winds. Representing a rare case of BAT in subcutaneous tissue, a 2 to 8 mm subcutaneous layer of BAT envelops their bodies. At a T_A of -11°C, the RMR of the neonate harp seal is about 150 kcal kg^{-1} daily, about triple that of other animals of comparable size. The gerbil (*Gerbillus compestris*), a mammal with a tolerance to low T_A (-20°C), is another example of the remarkable heat-generating power of BAT (20).

Marsupials and monotremes (noneutherian mammals) are regarded as having no BAT (21), although electron microscopy in marsupial macropods has revealed cells comparable to those of BAT of eutherian mammals (22). The FOK rat, a strain that was inbred for its resistance to heat, has low BAT activity (23) and secretes much more saliva from its submaxillary salivary glands than do other rat strains (24). The evaporation of each g H_2O from the saliva at 30°C causes a heat loss of 576 kcal (2421 kJ).

Leptin, a hormone secreted by white adipose tissue (25), contributes to homeostasis by suppressing food intake and increasing energy expenditure in proportion to body fat levels. The Zucker (fa/fa) rat is relatively insensitive to leptin (26) and exhibits a phenotype characterized by excessive food intake.

Fever

Fever, an increase in T_b that is usually associated with a microbial or viral infection, is not a failure of T_b regulation. It is part of a host defense response known as the "acute defense response" (27). The response includes a reduction in the plasma level of iron and zinc (28) and the release of "endogenous pyrogens," cytokines that induce fever. The first identified endogenous pyrogen was interleukin-1 (IL-1), a 15-18 kDa peptide, 1 of 25 known interleukins released from leukocytes and macrophages (29). Other known endogenous pyrogens are IL-2, IL-6, tumor necrosis factor (TNF), and interferons-$\propto$ and -β. Exogenous pyrogens, chiefly the 1000-kDa lipopolysachrides of bacterial cell walls (endotoxins), stimulate endogenous pyrogens to produce fever (30). The exogenous pyrogens are so potent that only 10^{-9} g of the purified endotoxin injected into a large mammal results in an increased T_b (30).

The pathophysiology of fever differs between the rabbit and the rat. In rabbits, interleukin-8 (IL-8) induces a febrile response that is inhibited by indomethacin, in contrast to its effect in rats. In rats, the pyrogenic effect of IL-8 is mediated by corticotropin releasing factor (CRF), whereas in rabbits, CRF attenuates the fever. Dexamethasone (0.5 mg kg^{-1}), a synthetic glucocorticoid, completely abolishes the febrile response induced by lipopolysaccharides and IL-8 in rats, but rabbits are less sensitive than are rats to the antipyretic effect of dexamethasone (31).

Antipyretic drugs, like aspirin, reset the "thermostat" in febrile mammals. In most mammals, such drugs have no effect if there is no fever or if the increased T_b is exercise- or T_A-induced. According to Nicholson and Altman (32), the rat is an exception. They report that sodium salicylate will reduce the T_b in the rat even if there is no fever, even when the T_A is as low as 5°C.

Although capable of producing a fever by shivering or peripheral vasoconstriction (33), squirrel monkeys (*Saimiri sciureus*) typically use a behavioral means of elevating T_b. After injection of prostaglandin E into the preoptic/anterior hypothalamic (PO/AH) area, these animals seek exposure to the sun or any warm location (33). Injection of leukocyte pyrogens into the PO/AH area of guinea pigs (*Cavia porcellus*) yields a similar response (34).

There are differences in cytokine-induced fever in obese (fa/fa) and lean (Fa/Fa) Zucker rats. Obese rats are much more responsive to IL-1 than are lean rats. The opposite is true for IL-6 (35).

Etiocholanolone, an intermediate metabolite of testosterone, is one of the few steroids that induces fever in humans and *Macaca mulatta*. Injecting 1.0 mg kg^{-1} into *M. mulatta* causes a thermogenic effect. In contrast, the injection of etiocholanolone into a squirrel monkey (*S. sciureus*) has no thermogenic effect, even at doses as high as 250 mg kg^{-1} (36). The New World monkey has no 5$\propto$- or 5β-reductase and is unable to act on etiocholanolone to form IL-1 (36).

Inflammation

Inflammation is a bodily defense reaction characterized by localized heat, redness, pain, and sometimes impaired function (37). Phagocytic cells (monocytes, neutrophils, eosinophils) interact with antigen-specific immune cells (T and B lymphocytes; 38). Prominent among the cytokines is interleukin-12 (39). These cytokines produce reactive oxygen species (the respiratory burst), along with lipid mediators (prostaglandins and leukotrienes) and proteases (40). These stresses incite the transcription of heat-shock genes and the synthesis of heat shock proteins. These proteins contribute to the defense against inflammation (41, 42), as does leukemia inhibitory factor (43).

Heat Dissipation

Heat is lost from the body by conduction, convection, radiation, and evaporation. Conduction takes place when physical bodies are in contact with each other; the heat travels from a region of higher to one of lower temperature. Convection refers to the transfer of heat when a fluid flows over a solid body or through a channel. Radiation is the loss or gain of heat by electromagnetic rays. The heat gained or lost by radiation depends on the color and the texture of an object as well as the temperature difference between objects.

A dominant feature of the response to heat in mammals is an increase in the blood flow to peripheral blood vessels, warming the body surface to increase the heat loss through radiation, aided by air or water currents (convection). Apical regions (ears, nose, lips, hands, feet, tails) are rich in arteriovenous anastomoses and, in response to heat, are enriched with blood reflexively by a loss of vasomotor tone (44). In non-apical areas (most of the body surface), heat causes a reflex active vasodilation (45). The active dilation is blocked by phenoxybenzamine, an $\propto$-adrenergic blocking agent (46). In the baboon (*Papio anubis*, 46) and the rat (*Rattus rattus*, 47) the peripheral blood flow to the skin and subcutaneous tissue before and after phenoxybenzamine administration does not differ (46, 47). This result provides strong evidence that the baboon and the rat respond to heat only by a reflex loss of vasomotor tone and not by active vasodilatation.

The rat (42), the muskrat (*Neofiber alleni*, 48), and the squirrel monkey (*S. sciureus*, 49) are species in which the flow of blood to the tail reflexively increases during heat stress. Heat dissipation occurs through the ears of the rabbit (50). Cattle (*Bos taurus*) and Pene David's deer (*Elaphurus davidianus*) are examples of animals in which the horns are involved in the dissipation of heat.

When stimulated by nitric oxide synthase (NOS), nitric oxide (NO), the endothelium-derived relaxing factor, dilates cutaneous blood vessels, warming the body surface and contributing to radiant heat loss and the control of sweating (50). NOS is inhibited by N-nitro-L-arginine-methyl ester (L-NAME, 51). By inhibiting the action of NOS, L-NAME administration may overheat an animal with serious consequences.

Evaporation is the most effective means of heat loss. It takes 100 cal to heat 1 g water from the freezing point to the boiling point, and 584 cal are required to change 1 g liquid water to water vapor at room temperature. The heat of vaporization varies a bit with the temperature, both T_A and T_b, at which

vaporization takes place; in the human, the temperature of sweating skin is about 35°C. The heat of vaporization at 35°C is 580 cal per g water, and at 25°C, the heat of vaporization is 585 cal per g water. A 100-kg animal would have to evaporate about 240 g water hourly to balance its BMR (8).

Heat loss by evaporation may take place by sweating, panting, or salivation and licking. Water continually diffuses through the skin (insensible perspiration) and from the lungs. During expiration, the movement of air over the mucosa, and some moisture condenses on the mucosa. This process causes the temperature of the expired air to be less than the body core temperature (52). In desert animals like the donkey (*Equus asinus*), camel (*Camelus dromedarius*), and the rat-kangaroo (*Bettongia caniculus*), this means of water conservation is considerable (53).

Humans, horses, cattle, and camels can sweat profusely; rodents, lagomorphs, pigs, dogs, cats, elephants, wildebeests, and gazelles cannot. (46). Of the two types of sweat glands, eccrine glands predominate in humans and secrete a hypotonic sweat that is about 99% water. Apocrine sweat glands, which develop from hair follicles and are the predominant sweat glands of horses and other domestic animals, secrete hypertonic sweat. Sweating is mediated by the sympathetic nervous system, although the receptor types differ between species. Eccrine sweat glands are stimulated by cholinergic receptors while being stimulated by adrenergic nerves (54, 55). Apocrine glands, at least in the horse, are stimulated mostly by β_2-adrenergic receptors (56).

Losses in sodium and other electrolytes occur during sweating, especially in the exercising horse (57). During panting, an evaporative cooling procedure used by most mammals other than horses, the tendency is to decrease the CO_2 tension in the blood to critical levels. Dogs and sheep use panting as their main means of evaporative heat loss. During a heat load, most of the air enters through the nose and leaves through the mouth (52). The unidirectional flow is effective in increasing the heat loss (52).

Some Species Differences in Response to Variations in T_A

The nine-banded armadillo (*Dasypus novemcinctus*), a bare-skinned, primitive type of mammal increases its T_b when subjected to a decrease in T_A (58). In marsupials, monotremes, and insectivores, the normal T_b is lower than it is in most other mammals. This difference is especially true of the echidna (*Tachyglossus aculeatus*), a monotreme whose T_b is typically about 31°C. A T_b of 37°C is lethal for the echidna (59).

Desert rodents, especially the spiny mouse (*Acomys cahirinus*), have evolved to have a T_b that is lower than that of most eutherian mammals (60). This condition is apparently due to decreased utilization of glucose, a condition that subjects the animal to hyperglycemia when fed in the laboratory, and to a 20% incidence of diabetes (60). The antelope ground squirrel (*Ammospermophilus nelsoni*), a diurnal desert rodent, exhibits a decrease in hypothalamic sensitivity when the T_A is decreased (61). Pronounced juvenile T_A rhythms exist in several strains of rats but not in rabbits (62). When subjected to severe heat, some large mammals, like the camel (*C. dromedarius*) and the hippopotamus (*Hippopotamus amphibius*), increase their T_b (63). For a 500-kg camel, a 7°C change in T_b corresponds to 2900 kcal of heat and a saving of 5 L of water that would be required to maintain a T_b by evaporation. The T_b can then be lowered during the coolness of the night (63).

Torpor

Torpor, including hibernation and estivation, has evolved in some mammals as a means of saving energy when the lower critical temperature zone of the mammal or bird has been exceeded and/or the food or water source is diminished. Torpor is an advanced form of thermoregulation and is not a reversion to primitive ectothermy (64). This process involves a resetting of the thermal center located within the subfornical organ in the vicinity of the hypothalamus (65).

Torpor may be seasonal or nonseasonal. Seasonal torpor may be manifested as hibernation (winter) or estivation (summer). Nonseasonal torpor can occur at any time, in response to a reduced T_A or a shortage of food or water (66). Seasonal torpor is controlled by circannual rhythm and is largely independent of T_A changes (64). In contrast, nonseasonal torpor is very sensitive to environmental changes (64). Many marsupials, like the murine opossum (*Marmosa cinerea*) and the crest-tailed marsupial mouse (*Dasycercus cristicauda*), have nonseasonal as well as seasonal torpor, a characteristic shared by bats (67).

Estivation is similar to hibernation (68). Both events may involve limitation of food and/or water availability. Estivation is usually an adaptation to hot, dry environments, whereas hibernation is primarily a response to cold. In estivation, a decrease in body water may serve as a trigger (68). When drinking water was restricted in deer mice (*Peromyscus arboreus*), they underwent a 25% decrease in metabolic rate and a 47% decrease in evaporative water loss. In the California pocket mouse (*Perognathus californicus*), behaviors such as avoiding predators, defending territory, burrow maintenance, and mating are regulators of torpor (69). Lack of these biological factors explain why some desert rodents fail to estivate in the laboratory when they do so in the wild (70).

Conclusion

Marked differences occur in the manner in which different species regulate their T_b. These differences must be taken into account when planning the construction of animal facilities and in the management of laboratory animal husbandry.

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