The physiology of heat tolerance in small endotherms

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Summary

Processes and patterns of heat tolerance vary widely among small endotherms, with far-reaching consequences for their occupancy of hot environments.

Abstract

Understanding the heat tolerances of small mammals and birds has taken on new urgency with the advent of climate change. Here we review heat tolerance limits, pathways of evaporative heat dissipation that permit the defense of body temperature during heat exposure, and mechanisms operating at tissue, cellular and molecular levels.

Introduction

Mass mortality events involving wild and domestic animal populations, as well as humans, are increasing in frequency and severity with rising temperatures and more frequent heat waves (90, 126). At a global scale, heat has become a significant natural killer of humans, with the first decade of the 21st Century seeing a 23-fold increase in human casualties from heat waves compared to the 1990s (7). Climate change projections suggest that, by the end of this century, in many regions of the world humans will be unable to safely move around or work outdoors (54, 57, 120).

Heat-associated mortality is also becoming increasingly evident among mammal and bird populations (79, 139). The capacities of animals to cope with extreme heat have been of interest to animal physiologists for decades. Although birds and small mammals are often thought to be buffered from extreme heat by virtue of their high normothermic body temperature (T_b), fibrous insulation and well-developed capacities for metabolic and osmotic regulation, rapid increases in global temperatures are increasingly challenging the thermoregulatory abilities of small endotherms (3, 82, 108, 139). The challenges of avoiding lethal hyperthermia may be most obvious in hot subtropical deserts where air temperatures (T_a) can exceed 50 °C, but they can also be pronounced in warm tropical lowlands where high humidity can severely limit evaporative heat dissipation, especially in species that forage in sunlit microsites (138) or occupy hot roosts during the day (68, 75). Even in much cooler regions at high latitudes, requirements for heat dissipation may pose substantial challenges and directly affect breeding success (101, 102).

The potential for even brief heat waves to drive catastrophic declines in mammal and bird populations is dramatically illustrated by recent events. In late November 2018, extreme heat in Australia's northeastern coastal city of Cairns killed approximately 23,000 grey-headed flying foxes (*Pteropus conspicillatus*), one third of the entire continent's population (59). This was just the latest catastrophic mass mortality event to affect the region's large pteropodid fruit bats, species with wing-spans approaching 1 m and which roost often roost in urban areas in colonies of hundreds to thousands of individuals. During the last decade, deaths by heat injury of large numbers of flying foxes (Figure 1) have become regular occurrences along Australia's east coast (139), with ~46,000 mortalities on a single day in January 2014 (108).

Figure 1. Dead black flying-foxes (*Pteropus alecto*) in southeast Queensland in the wake of a severe heat wave that killed an estimated 46,000 individuals in January 2014 (top), and heat-stressed juvenile grey-headed flying-foxes (*P. poliocephalus*) in the Sydney area in 2013 (bottom). Recent mortality events such as these illustrate how weather events during which air temperatures exceed physiological tolerance limits of most individuals in a population can – in a matter of days - cause the rapid demise and potentially regional extinction of species, specially those with slow reproductive rates. Photos: Justin A. Welbergen.

The causes of these mortality events are unambiguous; during recent events, widespread mortality was usually observed when T_a exceeded 42°C, a value that has subsequently been confirmed as a strong predictor of such die-offs (108). Flying foxes have daytime body temperatures that range from 37-39°C and typically do not permit body temperature to increase above 40 °C (8, 10), a narrow safety margin. When environmental temperatures approach or exceed body temperature, heats loads must be dissipated by evaporating water from the skin or respiratory surfaces, with rates of evaporative water loss increasing rapidly with increasing T_a. The short exposure times and rapid deaths observed during these heat-associated mortality events reveal that the flying foxes have a limited capacity for evaporative cooling and are consequently vulnerable to lethal heat injury. The relative roles of lethal hyperthermia arising from the bats being unable to dissipate heat rapidly enough *versus* exceedance of dehydration limits through long periods with rapid rates of evaporative water loss remain unclear, but both processes likely contribute to these now commonplace mortality events.

Our current view of thermoregulatory capacities in mammals and birds may be colored by our own superb abilities for coping with extreme heat. Well-hydrated, heat-acclimated humans standing in dry air can tolerate T_a exceeding 100 °C for brief periods (15, 93). Under these conditions, sweat glands can secrete upwards of 3 L of sweat onto the skin surface each hour (115, 133), with an associated maximum evaporative heat loss rate exceeding 2 kW. The ability to dissipate large environmental and metabolic heat loads in humans allows for sustained workloads at high T_a that range from four to six times basal metabolic costs (89). Among non-human mammals, comparable capacity for performance in the heat is limited to a subset of mostly large mammals, including camels (119), ungulates (41), felids (48), canids (1) and kangaroos (32).

The capacity of small endotherms to tolerate elevated T_b during heat exposure needs to viewed in the context of variation in normothermic T_b. The independent evolution of endothermy in mammals and birds is reflected by a number of broad physiological differences between these taxa. In mammals, normothermic T_b ranges from 30 - 41 °C, but with considerable variation among various groups (Figure 2; (25, 71). Birds show a higher but narrower range of active-phase T_b (37 − 44 °C), with an average of 41.0 ± 1.3 °C and higher T_b among songbirds (passerines) compared to other orders (24, 106).
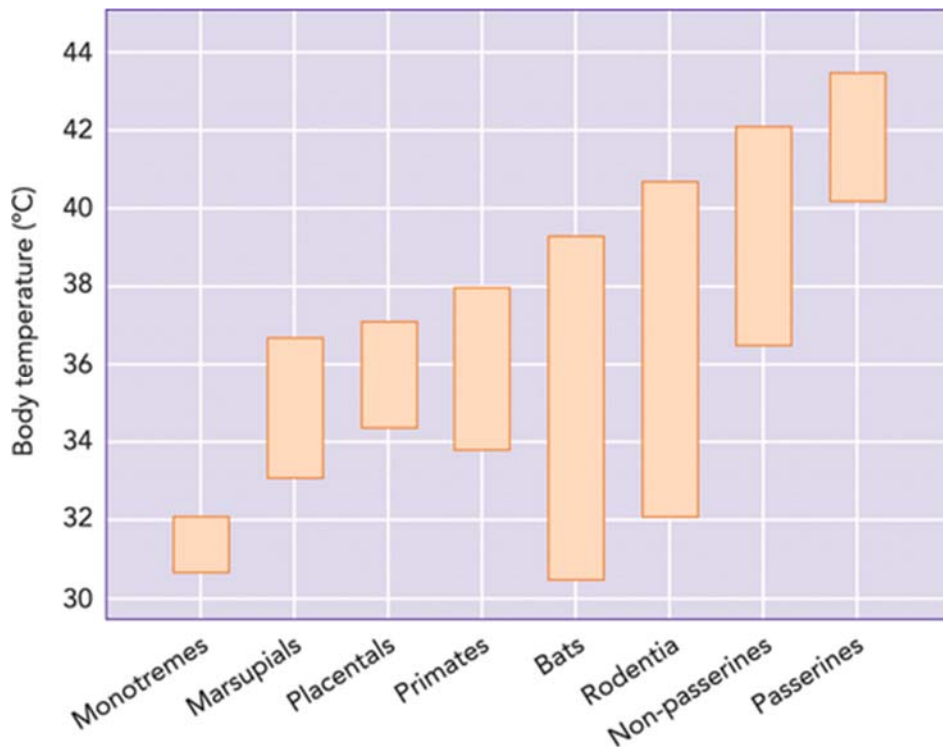
Figure 2. Variation in normothermic body temperatures among small endotherms. Placentals refers to average values for mammalian orders other than those shown seperately. Data from (24, 71).

Thermal tolerance – critical thermal maxima and lethal temperatures

Quantifying thermal performance and tolerance limits among endotherms is, in comparison to ectotherms, greatly complicated by the decoupling of T_b from environmental temperature. Body temperatures of ectotherms under experimental conditions largely track T_a and temperature limits are relatively easy to determine experimentally. The most commonly used assay, the critical thermal maximum (CTM, also referred to as CT_{max}) is used to estimate the T_b where thermoregulatory breakdown and tissue injury starts to occur (28). Critical thermal maxima are typically measured by exposing animals to progressively increasing environmental temperature, with loss of righting response or onset of muscular spasms considered endpoints in most studies (73). As originally defined, immediate cooling of animals that have reached their CTM allows for a reversal of damage and recovery (145). Although there is a rich literature on phylogenetic and ecological correlates of the critical thermal maximum (CTM) among insects (23) and among some groups of ectothermic vertebrates (Hutchison 1980), the literature examining CTM in small endotherms has, until recently, been limited to a few studies of rodents (Wright 1976; Erskine and Hutchison

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1982a, b) where rapid cooling at the CTM notably frequently resulted in survival of <50% of the study population.

A recent series of studies of avian thermoregulation in the heat has yielded body temperatures defensible as CTM values, being measured in birds that lost the capacity for coordinated locomotion or showed uncontrolled increases in T_b (140). Avian CTM varies from 43-46 °C, with some evidence for variation among taxa based on the thermal conditions in their natural habitats. Among arid-zone birds, CTM is typically $44 - 46°C$ (78, 81, 122, 125, 140) (Table 1, Figure 3). Although these and other studies (e.g., 131) suggest that birds can generally not tolerate $T_b > 46$ °C, a passerine from humid lowlands in Panama tolerated $46.8 - 47.0$ °C without any apparent adverse effects (138). Lethal T_b values of 46-48 °C have been reported for both poultry (4, 107) and wild birds (34).
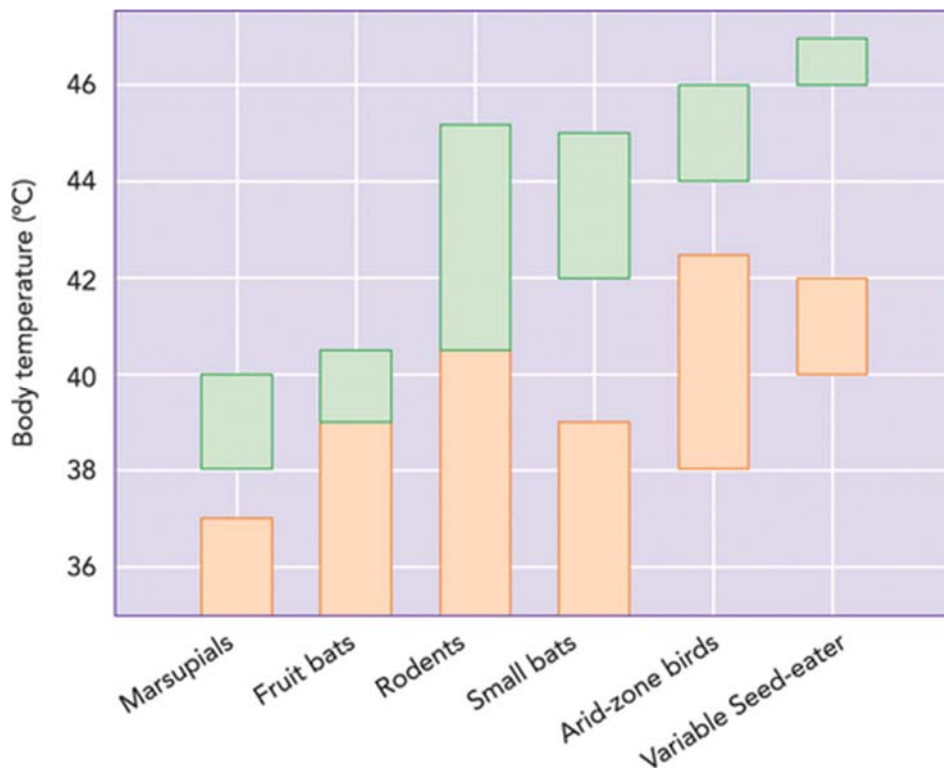
Figure 3. The approximate range of maximum body temperatures (T_b; red) and normothermic T_b (cyan) for various taxa of small endotherms. The maximum T_b values are from the sources cited in the text, as are the normothermic values for birds. Normothermic T_b values for mammalian taxa were obtained from Table 1 of (71). The data for *Sporophila aurita*, a small passerine bird that occurs in humid lowland habitats in Panama, were collected by Weathers (1994).

Table 1. Maximum body temperatures (T_b) for mammalian and avian taxa for which heat tolerance has been investigated. Asterisks indicate data that can reliably be considered critical thermal maxima (CTM) values.

Taxon	Maximum T_b (°C) * = CTM	Notes	References
Monotremes			
Platypus	38	Air temperature = 35 °C	(112)
Echidnas	~40	Can tolerate air temperature = 42 °C on occasion	(17)
Marsupials			
Pygmy-possum	40	Air temperature = 38 °C	(9)
Bandicoots	38-39	Air temperature = 40 °C	(53)
Kowari	39	Air temperature = 40 °C	(123)
Afrotheria			
Rock hyrax	41	Air temperature = 42 °C	(11)
Elephant shrew	40	Air temperature = 40 °C	(64)
Rodents			
Antelope ground squirrel	43.6-44.4	Air temperature = 48 °C	(21, 52)
Gerbils	43-44		(37)
Rabbits and hares			
Jackrabbits	43-44*	Air temperature = 50 °C	(118, 121)
Shrews and moles			
Shrews	< 40	Generally cannot tolerate air temperature > 35 °C	(36, 50, 70)
American shrew-mole	42.5	Air temperature = 33 °C	(19)
Bats			
Small insectivorous bats	~45		(27, 75)
Fruit bats / flying foxes	37-40	Air temperature = 35-40 °C	(8, 10, 63)
False vampire bat	41	Air temperature = 37 °C	(63)
Birds			
Arid-zone birds	44-46*	Maximum air temperature varies among taxa; typically 48-52 °C in passerines but 55 – 62 °C in columbids and caprimulgids	(78, 81, 122, 125, 140)
Variable seed-eater *Sporophila aurita*	46.8-47.0	Species from humid tropical lowlands in central America	(138)
Fynbos passerines	42-43.5	Air temperature = 38-40 °C. Species occurring in South Africa's fynbos biome	(86)

Among small mammals, CTM values and lethal temperatures appear to be broadly overlapping (Figure 3), with some variation related to taxonomy, acclimation history and measurement conditions. Small mammals' CTM and lethal T_b values were previously thought to range from 41 to 43°C (Adolph 1947, Brown 1968, Erskine and Hutchison 1982). Monotremes appear to have a very limited capacity for evaporative cooling (16) and modest tolerance of high T_b (Table 1), but microclimate measurements of logs within which echnidas spent the daylight hours revealed that they can tolerate T_a values as high as 42 °C (17). Among marsupials, early work on medium and large species suggested limited capacity to increase T_b much beyond 38 °C (e.g., 112), but less is known about heat tolerance in small marsupials. Among the handful of taxa that have been investigated, maximum T_b values during laboratory measurements were in the 38 - 40 °C range (Table 1).

The few data are available for small afrotherians suggest maximum T_b values of 40-42 °C (11, 64). Rodents typically have a greater capacity for hyperthermia, with the T_b of free-ranging antelope ground squirrels sometimes exceeding 43 °C (21). Jackrabbits from the arid US southwest can also tolerate high T_a, with T_b maxima in a similar range to those of rodents (Table 1). Shrews and moles have a very limited capacity to tolerate heat (Table 1); in some shrews T_a as low as 32 °C proved fatal after exposure of as little as 1 hr (36). Among small bats, early reported lethal T_b values varied from 41.9 °C to 43.5 °C (20, 67), but more recent work has documented T_b approaching 45 °C without any apparent adverse effects in small insectivorous bats (27, 75). Large bats such as flying foxes and false vampire bats appear to be less tolerant to high temperatures (Table 1).

The thermal tolerances of mammals and birds can also be considered from an environmental temperature perspective. CTM and lethal T_b represent the points at which heat injury occurs across multiple tissues and organ systems. Whereas these T_b values are broadly similar across many taxa, the maximum environmental temperature that an animal can tolerate varies more widely among species (Table 1) and with measurement conditions such as atmospheric humidity and exposure time. Atmospheric humidity values of $10 - 25$ g m^{-3} (equivalent to relative humidities at 40 °C of $25 - 50$ %) substantially inhibit evaporative cooling via reductions in rates of evaporative loss or increases in the metabolic rate required for panting (44, 105, 135). Exposure times can complicate estimates of heat tolerance especially in small animals where high rates of evaporative water loss rapidly lead to

dehydration and a reduced capacity for evaporative heat dissipation (5, 46, 51). Biological factors such as acclimation and acclimatization history also affect the maximum environmental temperature that allows the maintenance of a stable T_b (e.g., 95).

Among desert birds, environmental temperatures associated with the onset of thermoregulatory failure and loss of coordination are typically investigated under laboratory conditions, where birds are placed in darkened chambers and T_a and overall environmental temperature are approximately equal. Avian heat tolerance limits (i.e., maximum T_a before the onset of thermoregulatory failure) vary from 46 °C in an Australian honeyeater to 62 °C in the rock pigeon and common poorwill (78, 81, 127). Heat tolerance limits of 55-57 °C have previously been documented in other caprimulgids and bustards (35, 132), and heat-acclimatized rock doves can breed successfully at T_a = 60 °C (76). Less is known about heat tolerance limits in small mammals, but bats roosting in hot microsites such as under metal roofs typically start moving to cooler microsites T_a reaches 40-42 °C (18, 68), although they may sometimes encounter roost temperatures as high as 50 – 55 °C when roosting under metal roofs (47, 67).

**Whole-animal physiological responses**

The large differences among species in the maximum T_a at which effective thermoregulation is possible are strongly related to the primary pathway of evaporative heat loss and the associated metabolic heat load. Among mammals and birds, pathways of evaporative heat loss are broadly divisible into respiratory and cutaneous avenues, although evaporation across the exposed surfaces of the cornea (13, 103) and cloaca (49) may also be significant. The pelages of mammals and birds limit the extent to which thermal windows can be used to offload heat, and copious salivation and spreading saliva over body surfaces is a critical means of evaporative cooling for many mammals including rodents and large bats (31, 45); in kangaroos this cooling method supplements panting and involves licking of highly-vascularized regions of the skin (32, 94). A functionally analogous mechanism among long-legged birds such as storks and vultures is urohidrosis, whereby individuals defecate on their legs to augment cutaneous heat loss (6, 56).
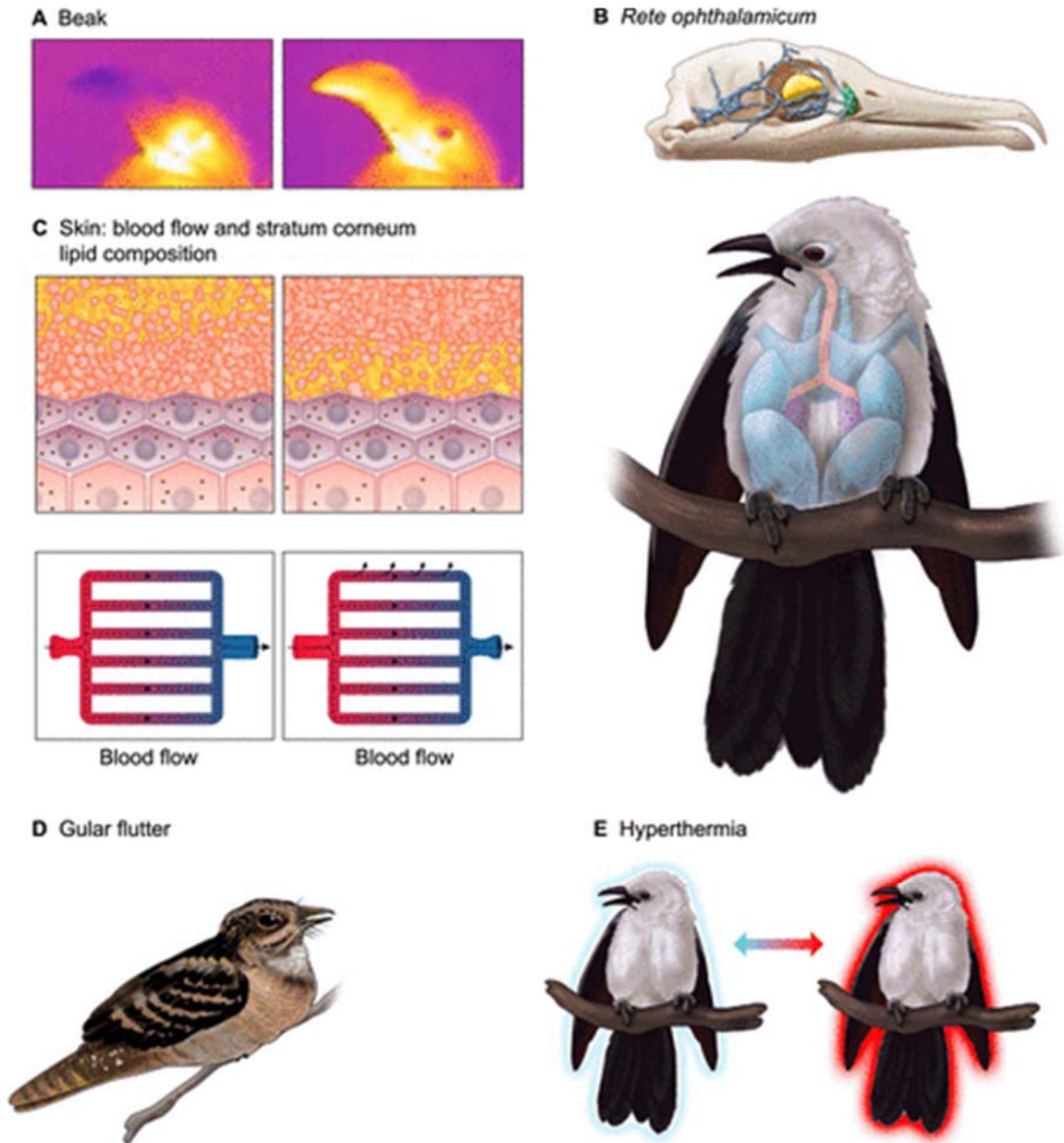
Figure 4. Heat dissipation occurs via a number of pathways. In a passerine bird, the primary avenue is respiratory evaporation heat loss by means of panting. Other mechanisms include a) the bill, which functions as a heat radiator when environmental temperature is still below body temperature, b) the *rete ophthalamicum*, a vascular structure that permits the maintenance of brain temperature below core body temperature, c) cutaneous evaporation, the rates of which are adjusted over short time scales via microvascular adjustments and over lower time scales though changes in stratum corneum lipid composition, and d) gular flutter, a rapid pulsation of the gular membrane that provides the basis for extremely efficient heat dissipation in groups such as the nightjars and allies.

The primary mechanism of respiratory evaporative heat loss in many mammals and most birds (Figure 4) is panting, which usually involves either a gradual or step-wise increase in breathing rate, typically to frequencies approximating resonant frequencies of respiratory systems, as well as reductions in tidal volume (109, 111). Under severe heat stress, however, respiratory frequency decreases and tidal volume increases (109, 111). The relative importance of panting as an avenue of respiratory heat loss varies among taxa. Panting appears to occur throughout the avian phylogeny (33), and is the dominant avenue of evaporative cooling among songbirds, which comprise more than half of extant bird species (110, 130, 143). Among mammals, panting is largely absent in rodents, but is pronounced in many larger taxa such as ungulates, macropod marsupials and canids (1, 142). An additional mechanism of respiratory heat dissipation widespread among non-passerine birds is gular flutter (Figure 4), the rapid pulsation of the gular region by the hyoid apparatus which leads to increased evaporation from the buccal cavity, pharynx and anterior esophagus, and which may interact with panting in several distinct ways (33).

Among many mammals, apocrine sweat glands provide the primary basis for elevating cutaneous evaporative heat loss in response to high environmental heat loads and/or activity-associated thermogenesis. As noted above, in humans and some other large mammals sweat glands are a highly effective pathway for heat loss in arid environments with low atmospheric humidity. Thermal sweat glands in humans are eccrine glands and differ from the apocrine glands responsible for sweat production in most small mammals mammals (14, 30). Heat-acclimatized humans can produce sweat at rates of > 3L hr^{-1} for several hours and the secretions are primarily water and small amounts of NaCl (0.2-0.3%), whereas the apocrine glands of other mammals have lower secretory capacities and may secrete a more complex salty fluid (40). The occurrence and distribution of sweat glands varies among taxa; they are absent in bats and limited to small areas such as footpads in rodents, felids and canids (40, 142). Among birds, cutaneous evaporation represents the major avenue of heat dissipation in some taxa, most notably pigeons and doves, with rates of cutaneous water loss regulated over short time scales via microcirculatory adjustments and over longer time scales via structural modifications to the skin (Figure 4, (84, 98, 99).
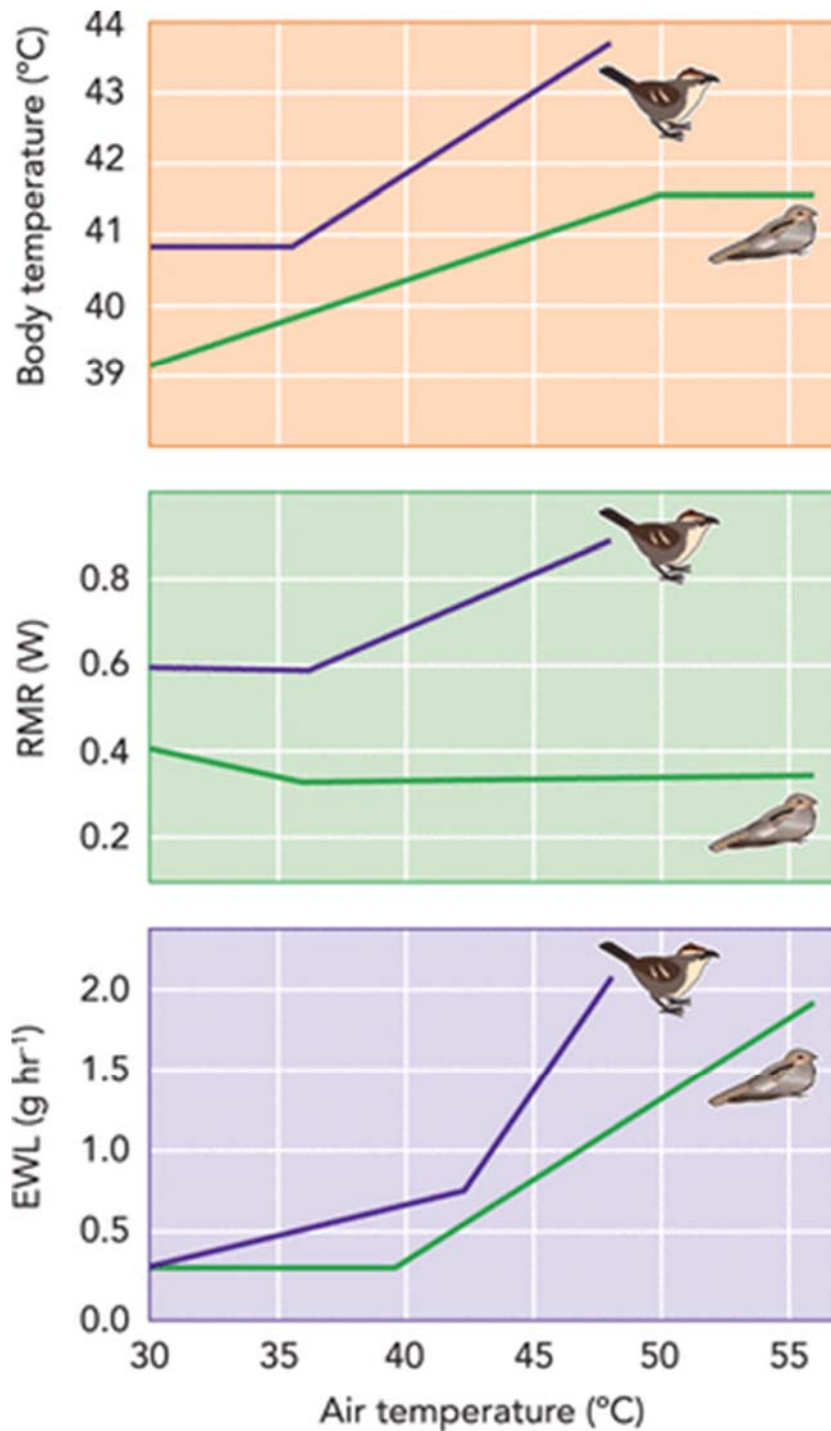
Figure 5. Relationships between body temperature (top panel), resting metabolic rate (middle panel) and evaporative water loss (bottom panel) in two ~52-g birds: the chestnut-crowned babbler (*Pomatostomus ruficeps*; blue lines) and the rufous-cheeked nightjar (*Caprimulgus rufigena*; dark red lines). In the nightjar, gular flutter provides the basis for dissipating heat with minimal metabolic cost, which allows this species to tolerate air temperatures ~ 6 °C higher than those reached by the babbler. In the latter species, panting predominates as an evaporative cooling pathway, and is associated with rapid increases in metabolic rate. Data for babblers and nightjars from (71) and (89), respectively.

Among birds, the primary avenue of evaporative cooling appears to have far-reaching consequences for the efficiency of evaporative cooling during heat exposure (Figure 5). In groups such as passerines that lack gular flutter or the capacity to greatly upregulate cutaneous evaporation, resting metabolic rate and thus total heat load increases steeply above the thermoneutral zone, sometimes to 2 – 2.5 X thermoneutral resting values (78, 80), and the maximum T_a tolerated during acute heat exposure is seldom above 50 °C (78, 125, 140). Taxa for which cutaneous evaporation or gular flutter predominate as mechanisms of evaporative cooling during heat exposure, on the other hand, show much shallower increases in metabolic rate (Figure 5), and can sometimes cope with air temperatures exceeding 60 °C (81, 97, 124, 127).

Most early work on EWL partitioning in mammals focused on the potential role of the skin in water conservation in desert species (117) or the role of saliva-spreading (45). Saliva-spreading may account for 60-70% of heat loss at T_a > 40 °C in rats (45), and is correlated with among-strain variation in heat tolerance (42). Intraspecific variation and phenotypic flexibility in cutaneous evaporation has been shown for arid-zone rodents (134), but in general less is known about cutaneous heat dissipation among small mammals compared to birds. One mammalian taxon in which cutaneous water loss has received attention is bats (22, 61, 87, 91, 137). During heat exposure, an African fruit-bat significantly increased both respiratory and cutaneous evaporation, with the majority of heat loss occurring cutaneously, except at T_a = 40 °C, when respiratory losses made up ~60 % of the total (87).

A vital component of both avian and mammalian responses to heat exposure is regulated hyperthermia, whereby T_b is permitted to increase above normothermic levels (33, 131). The functional significance of hyperthermia is primarily related to water conservation via three distinct processes. Among birds, the extent and functional significance of hyperthermia varies phylogenetically, with hyperthermia more pronounced in passerines compared to other orders (43). Birds routinely elevate T_b by several degrees above normothermic values in response to heat exposure (43, 131), and indeed may exhibit modal daytime T_b as high as ~43 °C and maxima exceeding 45 °C (129). Small mammals also generally permit T_b to rise well above normothermic levels during heat exposure (21, 72, 144).

Other tissue-level processes important to heat tolerance include brain-cooling mechanisms, such as the *rete opthalmicum* (RO) that appears to be a near-ubiquitous avian feature (Figure 4, (58, 85, 104) and the carotid rete in artiodactyls and felids (55). In birds, the RO provides the basis for maintaining brain temperature anywhere between 0.1 °C and > 2 °C below abdominal temperature (12, 29, 55). An additional avenue of heat loss that has attracted increasing attention in the last decade is the avian beak (Figure 4); in large-beaked taxa such as toucans, maximum rates of heat loss via the beak can be equivalent to 400 % of resting heat production (128).

Cellular and molecular processes

Heat stroke occurs when an animal's T_b exceeds the limits of normal function and results in damage to tissues and organs, with a cascade of hematological and immunological pathologies (66). It is produced by uncompensable heat stress where the thermoregulatory capacity of the organism is overwhelmed by an increasing metabolic and/or environmental heat load. The onset and progression of heat stroke is evidenced by, but not limited to, central nervous system disfunction, cell death, organ damage, coagulopathy, endotoxemia (associated with intestinal injury) (69) and the over-production of pro-inflammatory cytokines producing systemic inflammation (for mammals see (66); few data exist for birds (2).

Even sublethal heat exposure produces a heat shock response and promotes the expression of genes associated with the defense of cells (60). These responses are both rapid, appearing within 2.5 min of heat shock in mouse embryonic fibroblasts, and far-reaching with genome-wide up and down transcriptional regulation; in mouse fibroblasts, within one hour of heat shock ~ 1500 genes are upregulated and ~8000 downregulated with only a limited fraction of these induced by HSF1 (74). Although HSF1 is thought to be the "master regulator" of the heat shock response, most repression of transcription is independent of HSF1 and driven by reductions in RNA polymerase II pause release (74).

Among the most notable responses in the maintenance of proteostasis are the expression of genes regulating inducible heat shock proteins (HSPs), a highly conserved protein group notable for their wide range of functions in normal and abnormal environments (39). In both birds and mammals heat exposure induces the expression of a number of heat shock protein families (HSP 25, HSP 60, HSP 70, HSP 90, (60) (147). HSPs are believed to act by preventing protein denaturation or by processing protein fragments and

unfolded proteins (88, Richter et. al 2010). In addition to HSPs, the up-regulation of genes such as BCL-2 and VEGFA may also provide protection and the up-regulation of Interleukins may affect the inflammatory responses associated with heat exposure (147). The down-regulation of genes such as those associated with coagulation pathways (fibrinogen) may also benefit animals during extreme heat exposure.

The cellular effects of hyperthermia have received considerable attention in the context of cancer therapy, with exposure of mammalian cells to hyperthermic temperatures (typically 40-47 °C) resulting in a cascade of effects spanning cell membranes, cytoplasm, organelles and nuclei (reviewed by (62, 113, 136). Although there is limited evidence for exposure to high temperatures directly leading to changes in cell membrane composition, the thermosensitivity of mammalian cells increases with polyunsaturated fatty acid (PUFA) content (62), raising the possibility that facultative hyperthermia may, in general, be less pronounced in mammalian and avian taxa that make pronounced use of torpor or hibernation and for which PUFA is important for maintaining membrane fluidity at low T_b (114).

One major physiological system whose role in mediating the responses of small endotherms to heat exposure remains under-explored in a comparative framework is endocrine stress pathways, in particular the hypothalamic-pituitary-adrenal (HPA) axis. Elevated concentrations of circulating glucocorticoids (corticosterone in birds and either cortisol or corticosterone in mammals) are a well-documented response to heat exposure in poultry (38) and laboratory rodents (65). Among arid-zone birds, activation of the HPA axis in response to heat appears to occur in some species but not others (141, 146), and suppression of adrenocortical responses is important for facilitating breeding during the hottest parts of the year in very hot habitats (141). Other hormones known to be involved in responses to heat exposure in poultry include arginine vasopressin (stimulates water resorption by the kidneys and mobilizes free fatty acids), mesotocin, growth hormone, catecholamines, melatonin, reproductive and thyroid hormones (38).

Emerging questions and new directions

Earth is warming rapidly, and a better understanding of the physiological determinants of the direct effects of higher temperatures on small endotherms is vital for documenting and predicting their responses. In addition to quantifying variation among taxa in heat tolerance

and evaporative cooling capacity and elucidating the underlying functional mechanisms that differ among taxa, we need to understand the extent to which traits related to heat tolerance are phenotypically plastic.

There is evidence for phenotypic flexibility in traits such as the partitioning of avian evaporative water losses into respiratory versus cutaneous pathways (83, 92) and seasonal variation in heat tolerance (95, 132). In a southern African passerine bird, a population at a hot desert site significantly increased heat tolerance during summer compared to winter, whereas no such seasonal differences occurred in two populations at cooler, more mesic sites (95). The greater heat tolerance of the desert population in summer arose from more efficient evaporative cooling and lower T_b at a given $T_a > 40$ °C (95). This is one of only two studies of which we are aware to have examined seasonal acclimatization in avian heat tolerance, and much remains to be learned about the role of such phenotypic flexibility.

Among non-domesticated species, little is known about non-reversible phenotypic plasticity associated with developmental conditions. Recently, remarkable new insights have emerged into how, in birds, prenatal acoustic communication associated with hot incubation conditions may drive the subsequent expression of more heat-tolerant phenotypes among offspring (77). A potentially promising line of enquiry involves the experimental manipulation of environmental temperatures experienced by eggs and nestlings to elucidate the consequences of early heat exposure for tolerance limits and performance under hot conditions later in life.

Another suite of emerging questions concerns how thermotolerance at the cellular level and how mechanisms of cell protection translate into whole animal performance in the heat. The molecular bases for similarities and differences in thermotolerance among birds and mammals is also of significant interest. What, for instance, are the mechanistic bases for variation among taxa in lethal temperatures, both in terms of T_b and environmental temperature? Identifying the molecular bases for improved thermotolerance via phenotypic flexibility (acclimation/acclimatization to high environmental temperatures) or developmental plasticity will also provide information critical for understanding the limits to animals' capacities to respond to climate change. It is particularly relevant in species with generation times too long to evolve greater heat resistance (26) in the face of rapid anthropogenic climate change.

Finally, what are the weakest links in terms of specific tissues or organ systems in organismal thermotolerance in birds and mammals, and are these weakest links common across taxa? How do tissues differ in their susceptibility to heat injury, and are these tissue and organ systems defended in a such way that potentially allows for higher temperatures in other tissues? Such knowledge, combined with an understanding of the molecular basis of induced heat resistance, potentially opens the door to improvement of the weakest cell and organ systems via gene-editing technologies.

Anthropogenic climate change is advancing at a rapid rate, is already having pervasive impacts on natural systems (116), and is anticipated to drive catastrophic disruptions of ecological processes in coming decades unless urgent action is taken. In July 2018, Death Valley in California experienced four consecutive days with T_a maxima of ~52.8 °C during a month when the overall average 24-hr T_a was 42.3 °C (96). These maxima are several degrees above the maximum T_a values that several arid-zone passerine birds are able to tolerate (125). These challenges are not confined to hot deserts; warming in the Arctic is proceeding at twice the rate observed over the rest of the globe and warm extremes in these regions, although modest in terms of absolute temperatures, may have catastrophic consequences for species that are adapted to function at temperatures 10-20°C lower than have been recently observed (100). Unless urgent, concerted global action is taken, climate change may well create a future where many parts of the planet are habitable only for mammals and birds that have been genetically engineered to modify their heat balance (e.g. insulation, metabolic rate) or for enhanced heat tolerance.

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