Thermoregulation and aging

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Abstract

Accurate regulation of body temperature is essential for optimal function and survival. Elderly are at increased risk of both hypothermia and hyperthermia when exposed to extreme temperatures. Two new investigations show that it does not take extreme temperatures to see differences between the aged and the adult. In this issue of the American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, DeGroot and Kenney (9) showed in humans that core body temperature dropped already with mild ambient cooling in the aged, while it remained high in young subjects. This finding provides support for a deficit in autonomic thermoregulation, even with mild cooling. The drop in core body temperature, however, was not compatible with heat loss as calculated with a model on the measured variables, suggesting that the presently adopted models may require adaptation for aging studies. We suggest that it may be of value to evaluate whether the ratio between core and shell body compartments, as proposed by Aschoff and Wever (2), could help to solve the discrepancy between observed and modeled heat loss in elderly. Moreover, we propose that the cutaneous blood flow and temperature of the extremities of the body require a closer examination. Although these parts are rich in arteriovenous anastomoses and therefore extremely well suited for heat loss regulation, their temperature is usually hardly, if at all, present in calculations of mean skin temperature and heat loss to the environment. Not only core and shell modeling, but also distal skin measurements may improve our understanding of age-related deficits in autonomic thermoregulation. In a non-human primate model, the mouse lemur, Aujard et al. (3) showed that also behavioral thermoregulation changes with age. Selection of ambient temperature was studied during the inactive (daytime) and active (nocturnal) circadian phases, both during a long photoperiod (simulated summer season) and a short photoperiod (simulated winter season). Old animals selected significantly higher ambient temperatures than adult animals in all conditions, except when it was needed most: during the ‘winter days’, i.e. the period during which both the circadian and the seasonal phase dictate a low activity level, and, moreover, ambient temperature is normally low. This suggests that aged animals, although in general seeking higher ambient temperature, may not optimally utilize photoperiodic information to adapt behavioral thermoregulation, which has to be confirmed in future studies.
Humans need to regulate their body temperature within restricted limits in order to function well, and even more essential, in order to survive. Epidemiological studies suggest that most of the deaths due to hypothermia or hyperthermia occur in elderly subjects (4, 6, 8). The reason why especially the elderly are at such an increased risk of thermoregulatory deficits is not a new question, yet still important and not solved. Is it because their capability to sense temperature is compromised, because their thermoregulatory capacities are limited, or because their physiology is less tolerant to endure extreme temperatures? Previous studies suggested that probably all these possibilities contribute in case of extreme temperatures. Age-related changes, however, may also occur under less extreme temperatures (reviewed in 22). Investigation of thermoregulation in the range of mildly elevated or decreased ambient temperature is of importance, because even small changes in body temperature may strongly affect basal functions including vigilance (16), and because in most of the fatal or near-fatal cases the exposure to extreme ambient temperatures will be preceded by exposure to mildly elevated or decreased temperatures. If thermoregulation does not start in time during the drift from thermoneutrality, it may be more difficult to make up for body cooling or heating at a subsequent phase of extreme ambient temperature. Two new reports now specifically address the issue of age-related changes in thermoregulation in a non-extreme range of ambient temperatures. The first study, reported by DeGroot and Kenney (9) in this issue of the American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, demonstrates age-related deficits in autonomic thermoregulation in humans. The second study, of Aujard and colleagues (3), shows that in a non-human primate model age-related changes in behavioral thermoregulation differ depending on the season and on the circadian phase or sleep/wake state.

DeGroot and Kenney (9) confined a quite respectable number of thirty-six young and forty-six aged subjects to a semi-recumbent position and exposed them to an ambient temperature that slowly drifted downwards from thermoneutrality. Meanwhile, continuous assessments were made of skin temperature, skin and forearm blood flow, arterial blood pressure, oxygen consumption and subjective thermal sensation. Subjects were exposed just until sustained involuntary shivering occurred, which was
after a median duration of about 80 minutes for both young and elderly subjects. Although this finding at first sight might suggest integrity of at least the autonomic shivering response, group differences in core body temperature actually indicated that the shivering response occurred at a much lower core body temperature in elderly subjects. At baseline, core (esophageal) temperature was slightly, near-significantly, lower in the elderly subjects, and metabolic heat production significantly lower. Importantly, whereas the young subjects could maintain their core temperature during the ambient cooling protocol, elderly could not, and showed a progressive decline to almost 0.2 below their baseline value by the time shivering set in. Now what could have been the reason for the drop in temperature in elderly subjects? An obvious assumption is that it has to be a dysbalance of the ratio between heat production and heat loss. Indeed, elderly subjects had a lower metabolic heat production and an attenuated cutaneous vasoconstrictor response to the cold exposure.

The puzzling thing about the results was, however, that biophysical modeling according to the present standards could not account for the findings, because heat production in elderly subjects was already lower at baseline, and because heat loss appeared to be similar between groups. The discrepancy suggests that it may be necessary to re-evaluate the models applied, or reconsider the way the variables entered into the model are estimated. DeGroot and Kenney did an impressive effort by evaluating a more refined model for the thermometric determination of changes in body heat, which includes a ‘mid-region’ for heat distribution. The model did not solve the clear discrepancy between the observed drop in body temperature versus the predicted unaltered body temperature. The idea of several regions in body heat content is not new. Some 50 years ago, Aschoff and Wever (2) described the concept of a core and a shell, which could vary in their relative size. The core includes the organs that generate heat, which is redistributed convectively towards the shell through the blood flow. The outer part of the shell, i.e. the skin, can exchange heat with the environment. The size of the shell determines the heat exchange with the environment. In a cooler environment, the size of the shell increases to insulate the core from heat loss to the environment. Perhaps this concept could bring us closer to the understanding of the discrepancy. It is conceivable that heat flow from the core to the skin changes with aging. As done in many studies,
DeGroot and Kenney calculated heat loss from the difference between skin and ambient temperature. However, others have argued that this difference should be divided by the gradient between the core body and ambient temperature, to better represent heat flow from the core to the environment. Since the core body temperature of elderly was somewhat lower, the heat loss index would be higher in elderly than in young subjects if this calculation had been used. A novel technique, i.e. proton resonance frequency (PRF) magnetic resonance temperature imaging (10, 14, 20) promises the possibility to investigate whether elderly subjects may indeed have a reduced retraction of shell blood flow under cold stress conditions. If so, such attenuated increase in the size of the insulating shell might account for their compromised heat conservation. In addition, the contribution of age-related changes in the constitution, microvasculature and thickness of the skin itself (12, 24) should be considered, since it is the outer border of the shell where the heat flow to the environment ultimately takes place.

Consider heat loss due to radiation and convection, which is defined as the difference between skin temperature and ambient temperature, multiplied by a coefficient. As often done, DeGroot and Kenney calculated a single mean skin temperature as a weighted sum of several areas of the skin. The distal parts of the body are usually hardly represented as such. It has, however, already been recognized by Aschoff (1) that the distal parts of the body may be the more important heat loss effectors of the shell. The palmar sides of the hands, plantar sides of the feet, ears, lips cheeks and nose tip contain arteriovenous anastomoses (AVA’s, reviewed in 22). These shunts between the arteries and the venous plexus are regulated through sympathetic innervation and little responsive to changes in local skin temperature. If opened, they strongly increase the local skin blood flow, and thus ultimately heat transfer from the core to the environment. In human and animal studies, the skin areas where they are present have been recognized as specialized heat exchanging areas, also because these areas have a high surface-to-volume ratio, an absence of fur and a dense network of blood vessels (18). Examples of such heat exchangers other than the human hands and feet are the rabbit ear and the rat tail. Under ambient temperatures close to and including thermoneutrality, the major interest of the papers discussed here, these are the only areas of the body that control sensible heat loss.
Because the AVA-rich distal areas of the skin are so conductive for heat loss, the fact that these areas have been virtually left out of the mean skin temperature calculation may have resulted in an underestimation of the actual heat loss. That is, if we suppose elderly to have an attenuated distal vasoconstrictor response, resulting in an attenuated drop in distal skin temperature, and therefore a deficient shielding from heat transfer from the distal skin to the environment. Could the discrepancy between the biophysical model on heat loss and the actually observed decrease in core body temperature in elderly subjects be due to such underestimation of actual heat loss? A previous study suggests that this may indeed be the case. Frank et al. (11) measured core temperature, skin temperature and finger blood flow responses to cold infusion. As compared to young subjects, elderly subjects maintained a much higher blood flow in the fingertip, the very area with the most dense presence of AVA’s. This finding suggested an attenuated prevention of heat loss from the extremities in elderly. Indeed, core body temperature dropped more in the elderly than in young subjects. Meanwhile, of note, Frank et al., like DeGroot and Kenney, also failed to observe a difference between young and old subjects in mean skin temperature decrease, which was also calculated without including distal sites. Although the studies differ in many aspects and no definite conclusion can be drawn, they leave open the possibility that elderly, when exposed to ambient or core cooling, may have selective deficits in preventing heat loss from the AVA-rich extremities. This would have to be confirmed in mild ambient cooling studies including distal skin temperature and blood flow measures in addition to the habitual mean skin temperature based largely on more proximal sites.

Thermoregulation does not only rely on responses of the autonomic nervous system. Behavioral thermoregulation may even be more important for survival. For example, rats respond to an elevated environmental or core temperature by grooming to promote evaporation, locomotion to find a cooler place, and postural extension to reduce muscle activity heat production and promote heat loss by increasing the body surface area (17). Thermoregulatory behaviors may show a strong circadian and sleep-state related modulation: under constant ambient temperatures rats for example curl up to prevent heat loss
if they prepare for sleep (22). If not confined to laboratory restrictions, as in the study of DeGroot and Kenney, aging studies that allowed for behavioral thermoregulation have revealed that aged animals may compensate autonomic thermoregulatory deficits by behavioral thermoregulation. An example is that aged rats show a blunted fever response to lipopolysaccharide (LPS) injection if they are kept at an ambient temperature (Ta) of 23 °C, but if allowed, they select a higher ambient temperature than young rats do, and in this way still accomplish the wanted increase in body temperature (15). Humans also strongly depend on behavioral thermoregulation. Unfortunately, the number of controlled studies on age-related changes in behavioral thermoregulation under ambient temperatures that deviate only mildly from thermal neutrality is even lower than the already very limited number of studies focusing on autonomic thermoregulation under such mildly deviating conditions (22). The reason for such lack of data may be found in the elaborateness of realistic experiments in humans. Non-human primate models may be of use here. In a recent study, Aujard and colleagues (3) demonstrated that age-related changes in the behavioral thermoregulation of mouse lemurs do not only occur with exposure to thermal stress, but also during everyday thermoregulation. Moreover, that such thermoregulatory behavior depends on the phase of circadian and seasonal cycles. The mouse lemur lives up to about 10 years, during which period it shows many similarities to the aging process of humans, including cerebral atrophy, cognitive decline and hormonal changes. Also the fragmentation of the circadian locomotor activity rhythm is remarkably similar to what is observed in human aging and dementia (7, 13). The mouse lemur has even be proposed as a major model for Alzheimer’s disease (5).

Aujard and colleagues placed adult and aged animals in a cage where they were free to stay in any of five small chambers of different temperatures (10-30 °C). A number of important new findings were reported. First, aged animals generally selected higher ambient temperatures, while their core body temperature is lower. This suggests that the aged animals may compensate for possible autonomic thermoregulatory deficits by choosing higher ambient temperatures than young animals. Second, the selected ambient temperature strongly depended on both season and time of day. During the night, the major active (awake) period of this diurnal species, the selected ambient temperature was not affected by
photoperiod length (season). In contrast, during the day, the major period of inactivity and sleep, the selected ambient temperature was higher during the short photoperiod. Although this response was preserved in aged rats, their relative increase in selected ambient temperature as compared to the daytime temperature selection during a long photoperiod was three times less (+1.3 °C) than the response of adult (+3.9 °C) animals. Selecting a higher ambient temperature for the sleep period during the short photoperiod makes sense, because a short photoperiod (‘winter’) is associated with a colder environment and an overall reduction in physical activity, and the sleep period is also associated with little activity: a combination of three factors that may increase the risk of hypothermia. But, in fact, aged animals choose higher ambient temperatures than adult animals under all conditions except when it seems most needed – during the inactive diurnal sleep period of the ‘winter’-time, when core body temperature is lowest. In other words, although aged animals in general choose higher ambient temperatures, possibly to compensate for suboptimal autonomic thermoregulation, their compensation may fall short when it is most needed, i.e. when the nights are cold and long. This finding suggests for the first time that the utilization of photoperiodic information to modulate thermoregulation is compromised in aged animals, which is an important contribution to the known age-related changes in the response to light (23).

Behavioral thermoregulation with a clear diurnal modulation is also utilized on a daily basis by humans. During the nocturnal sleeping period, humans use bedding covers to create a microclimate, and concomitant skin temperature of about 34 °C, which is much higher than the temperature reached during daytime (19, 21). It would be of great interest to investigate age-by-daytime-by-season interactions in humans, specifically whether aged humans show season-dependent deficits in the regulation of their nocturnal microclimate. Micro-loggers for naturalistic studies are available and have been validated (19). Such investigation may not only provide insight in risk factors for hypothermia. It may as well learn us more about disturbed sleep in the elderly, because it was recently demonstrated that even a very small decrease of skin temperature attenuates sleep propensity, i.e. the pressure to fall asleep (16). Even a slightly lower microclimate temperature might thus contribute to the nocturnal awakenings that elderly so frequently suffer from.
To summarize, the two recent studies discussed here show a number of important issues. First and foremost, they demonstrate the importance of investigating age-related changes in autonomic and behavioral thermoregulation under non-extreme thermal circumstances. Second, the human study suggests that it may be worthwhile to include the core and shell concept in heat loss models, as well as to include data on the skin blood flow and temperature of the AVA-rich distal parts of the body. Third, the studies suggest that it is plausible that elderly compensate autonomic thermoregulatory deficits with behavioral thermoregulation, i.e. by seeking higher ambient temperatures, which has to be confirmed in naturalistic studies. Fourth, the mouse lemur study shows that age-related changes in thermoregulation may be modulated by the circadian and seasonal phase. Finally, the mouse lemur study also suggests that aged animals may not optimally utilize photoperiodic (day length) information to adapt their thermoregulation. These exciting new findings and suggestions warrant further investigation.

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