Modulation of thermogenesis and metabolic health

doi: 10.1111/obr.12789

Review

Modulation of thermogenesis and metabolic health: a built environment perspective

W. D. van Marken Lichtenbelt[1], H. Pallubinsky[1] and M. te Kulve[1,2]

[1]Department of Nutrition and Movement Sciences, NUTRIM Maastricht University Medical Center, Maastricht, The Netherlands; and [2]BBA Binnenmilieu, The Hague, The Netherlands

Received 7 September 2018; revised 13 September 2018; accepted 13 September 2018

Address for correspondence: WD van Marken Lichtenbelt, Department of Nutrition and Movement Sciences, NUTRIM Maastricht University Medical Center, PO box 616, 6200 MD Maastricht, The Netherlands.
E-mail: markenlichtenbelt@maastrichtuniversity.nl

Summary

Lifestyle interventions, obviating the increasing prevalence of the metabolic syndrome, generally focus on nutrition and physical activity. Environmental factors are hardly covered. Because we spend on average more that 90% of our time indoors, it is, however, relevant to address these factors. In the built environment, the attention has been limited to the (assessment and optimization of) building performance and occupant thermal comfort for a long time. Only recently well-being and health of building occupants are also considered to some extent, but actual metabolic health aspects are not generally covered. In this review, we draw attention to the potential of the commonly neglected lifestyle factor 'indoor environment'. More specifically, we review current knowledge and the developments of new insights into the effects of ambient temperature, light and the interaction of the two on metabolic health. The literature shows that the effects of indoor environmental factors are important additional factors for a healthy lifestyle and have an impact on metabolic health.

Keywords: Light, metabolic health, thermal comfort, thermophysiology.

Introduction

Nowadays, international and national agencies provide advice concerning healthy dietary patterns and guidelines for physical activity. No doubt, adherence to each of these traditional evidence-based guidelines will lower the risk of many non-communicable diseases that are related to obesity and the metabolic syndrome. However, prolonged adherence to these beneficial changes in lifestyle is often low and recidivism is very common, e.g. Dunstan *et al*. and King *et al*. (1,2). It is our impression that a multimodal approach is expected to lead to a higher success rate (3,4).

The impact of novel environmental lifestyle factors in the built environment on metabolic balance, such as ambient temperature and light exposure (both intensity and colour), is nowadays still largely neglected. This underappreciating occurs not only in the built environment sector but also in the field of health education. In the built environment sector, the attention is mostly focused on energy savings, energy transitions and sustainability with respect to the utilized materials (e.g. adhering to the Breeam certificate). Although there is an increased attention to role of the built environment in health issues, as nowadays seen by the Well Building Standard, little inclusion of current knowledge on the achievements of the effects of ambient temperature and light exposure on metabolic health is realized.

At least two reasons for this can be identified: First of all, results from laboratory-based studies are published in journals not familiar to the built environment community, and the other way around, the 'metabolic community' is not familiar with the recent developments in the built environment. The other reason is that there is need for more information on how a combination of the various factors can influence metabolic health.

Clearly, an overwhelming amount of research is published on diet and physical activity. Also, an increasing amount of knowledge has been gathered on the separate effects of light and ambient temperature. However, research

on how a combination of certain light and ambient temperature conditions might contribute to a healthier indoor environment has hardly been carried out. In this paper, studies on the effects of temperature and light exposure on thermophysiology and the potential health aspects will be reviewed and future perspectives will be presented.

Ambient temperature

Most thermophysiological studies describe the effects of rather extreme temperatures on human physiology, and this information can also be found in the textbooks. De facto, in our daily living conditions, these temperatures are rarely experienced. However, we are frequently exposed to more mild deviations from our thermoneutral temperatures in day-to-day life. Thermoneutral refers to the so-called Scholander model, where the thermoneutral zone is defined as the range of ambient temperatures without regulatory changes in metabolic heat production or evaporative heat loss (*5*). The lower critical temperature defines the lower bound of the thermoneutral zone, below which heat production is increased by shivering and/or non-shivering thermogenesis (NST) to maintain thermal balance. The upper critical temperature has two definitions: firstly, it is the ambient temperature above which sweating is initiated and, secondly, above the upper critical temperature, metabolic rate increases as a result of the inability to dissipate enough heat. Body temperature then rises and metabolic rate increases via Q10 effect combined with increased ventilation and heart rate. Even mild cold and heat exposures are usually avoided in buildings (dwellings, care centres and offices) having a tightly controlled indoor climate as determined by the ASHRAE Standard 55 and ISO Standard 7730. These standards are based on Fanger's predicted mean vote model, which assesses thermal comfort in occupants (*6*). The application of this model has often led to a uniform indoor climate. In practice, this means that throughout the day, during all seasons, and from the tropics to the arctic regions, approximately the same indoor conditions are established, although nowadays the adaptive comfort model is increasingly applied (see succeeding texts).

These indoor temperature standards are calculated around the assumption of an 'average occupant' and have the goal to maximize thermal comfort. Oftentimes, however, the application of these guidelines leads to complaints from the users about the temperature and also results in high energy bills. Another issue is that the indoor climate is fixed around a presumed mean comfort temperature, but in reality, the average occupant does not exist and therefore the thermal environment is likely to be perceived differently by different users (*7*). For example, men and women have different thermal needs which are, amongst other things, based on differences in metabolic rate. Women generally have a lower metabolic rate, which is why they usually prefer warmer thermal environments than men (*7*). Moreover, differences between individuals due to other factors such as body composition, age and the level of acclimatization are important modulators of thermal perception but are not accounted for in the traditional comfort models.

Importantly, due to the application of the traditional standards and the resulting small variation of the indoor climate, the human thermoregulatory system is much less challenged to maintain a constant body core temperature. This affects our metabolism and makes occupants vulnerable to temperature variations. More frequent exposure to heat and cold can affect our metabolic health and may create more resilience to these deviant temperature conditions. Indeed, field studies show that people adapt to climatological, seasonal and daily variations in temperature and tolerate a much wider range of temperatures than prescribed by the predicted mean vote model. Based on this knowledge, the adaptive comfort model was developed (*8,9*), which nowadays is included in the ASHREA standard 55. Application of this adaptive model results in a more dynamic indoor climate and also leads to lower heating and cooling costs. However, physiological parameters and health aspects are also not specifically included in the adaptive model, which underpins the need for further development of modern indoor climate standards.

Cold

Being exposed to temperatures outside the thermoneutral zone affects human heat loss parameters and heat production. Cold can induce an increase of our energy expenditure by shivering, due to repeated fast muscle contractions. Shivering thereby increases heat production. It should be noted that heat production is identical to energy expenditure. During shivering, energy expenditure can easily rise by 300% of resting metabolic rate (*10*). During acute cold exposure, not only the muscle contractions are sustained by the combined oxidation of carbohydrates, lipids and protein, but also intramuscular glycogen reserves are used as a metabolic substrate (*11*). During longer term cold exposure, lipids are by far the predominant fuel source, providing substrate for 80% of the heat produced after 12 h in the cold (*12*). Other studies also suggest that regular severe cold exposure may stimulate insulin sensitivity, as observed in cold water swimmers (*13*). Importantly, shivering leads to fatigue, reduces coordination and is uncomfortable. Shivering is therefore difficult to sustain over a longer period of time and is generally judged unacceptable. For practical application, shivering-induced energy expenditure might potentially be used as a therapy but is not suitable to help burn more calories in daily living circumstances.

Interestingly, already in the 80s, it has been shown that exposure to mild cold can significantly increase whole-body daily energy expenditure by means of NST (*14,15*). In

contrast to shivering, NST functions without muscle contraction, is less uncomfortable and may even be judged acceptable, especially after regular exposure to mild cold conditions. The increase of thermogenesis (without noticeable shivering) can yet be substantial – up to 40% of resting metabolic rate (16) – but significant individual variation is evident (17). In some people, especially the elderly, mild cold exposure has been shown to even reduce rather than increase energy expenditure. It is not yet sure whether this is caused by 'biological' ageing or by a lack of exposure to variable temperatures, as elderly are generally even less exposed to cold than younger people. Most likely it is a combination of these factors. It is well established that physically fit older people also have improved thermoregulation compared with less fit elderly (18). Not only the elderly but also people with obesity also have a blunted response of cold-induced thermogenesis compared with lean people of the same age group (19).

Interesting in this respect is that with the onset of modern imaging techniques, active brown adipose tissue (BAT) was detected in patients in 2002 (20,21). In 2009, several research groups showed the presence of functional cold activated BAT in healthy adult humans (22–25). BAT is the tissue responsible for NST in rodents, in several species of hibernators and also in human babies (26). In rodents, it appears to be a very flexible tissue and is more present and active when needed, for instance, in the colder winter season (27). In adult humans, its presence was well known from older anatomical studies (28,29), but with the onset of modern imaging techniques from nuclear medicine, it was possible to show functional cold-induced brown fat in adults. The technique most widely used nowadays is Fluorodeoxyglucose^{-18}F Positron Emission Tomography/Computed Tomography (FDG-PET/CT) (30). For more details of other techniques to assess BAT in humans, see Chondronikola *et al*. (31). It is, however, important to realize that with this technique, the uptake of glucose in the tissue is measured, not the total amount of energy metabolism of BAT.

The activation of brown fat is known to increase metabolism, by means of uncoupling the electron transport chain. Crucial for this uncoupling mechanism is uncoupling protein 1. This protein is located on the inner membrane of mitochondria, the latter being present in large amounts in brown adipocytes. When BAT *is not activated*, it uses the proton-motive force to synthesize adenosine triphosphate (ATP), just like most other cells do. However, when BAT *is activated*, uncoupling protein 1 short circuits the proton gradient across the inner membrane of the mitochondria and instead of adenosine triphosphate, heat is produced. BAT activity appears to be correlated with NST and is reduced in subjects with obesity (32) and elderly (33) which is in line with the above-mentioned studies on NST in elderly and subjects with obesity. BAT is not only a thermogenic tissue but also capable of disposing large amounts of lipids and glucose. Therefore, BAT is regarded as an important factor in metabolic health (11), and a potential target for the prevention and treatment of obesity and type 2 diabetes mellitus (T2DM).

Interestingly, in a weight reduction intervention study in subjects with morbid obesity, we showed that BAT is a flexible tissue, demonstrated by the fact that its activity and volume could be increased after weight loss (34). A logical next step after this finding was to perform a cold acclimation study and to investigate the effect of repeated cold exposure on BAT. Early studies in humans already showed increases of NST after cold acclimation (35) and indeed, we and others showed that after a period of regular cold exposure, BAT's presence and activity significantly are increased in both male and female subjects (36) (37). In parallel, also the NST capacity increased, which was positively correlated with the increase of BAT activity. In one cold acclimation study (2-h cold exposure per day, at 17°C for 6 weeks), the amount of white fat was even shown to decrease (38). Based on this previous knowledge, we also carried out acclimation studies in people with obesity and patients with T2D. Again, an increase of brown fat activity and NST was evident, although the amount of BAT detected in the T2D patients was generally very low (39,40). Due to the limitations of the commonly used imaging techniques (measuring glucose uptake in BAT), it is not yet known what the actual quantitative contribution of human BAT to NST is. Especially in patients with T2D, the insulin sensitivity of BAT and thereby also the uptake of glucose can be reduced. Remarkably, Hanssen *et al*. showed that mild cold acclimation actually also increased peripheral insulin sensitivity in patients with type 2 diabetes (39). The tissue responsible for this result most likely is skeletal muscle, as a significant translocation of glucose transporter type 4 (GLUT4) to the membrane of muscle cells was evident post-acclimation.

All in all, prolonged exposure to mild cold shows the potential to contribute to both weight maintenance and glucose metabolism (see also Lee *et al*. (41)). It may very well be the case that both cold-induced BAT activity and skeletal muscle activity contribute to increased thermogenesis and improved glucose metabolism.

Besides energy and glucose metabolism, cold may also affect lipid handling and thereby the cardiovascular system. Although most studies focus on measuring the glucose component of BAT substrate use, which is due to methodological limitations, active BAT actually uses fatty acids as main substrate (26). BAT cells contain lipid droplets that contain triglycerides (42). Activation of BAT through cold leads to an increased density of BAT tissue on CT scan images, indicating lipolysis of these intracellular triglyceride-containing lipid droplets (43,44). In addition, recent research shows that after cold exposure, plasma levels of free fatty acids and glycerol increase, indicating increased lipolysis in white adipose tissue and the release of these lipolysis products into the

bloodstream (45). The implicated mechanism is that when the storage of lipids inside brown adipocytes is depleted, active BAT takes up free fatty acids from the blood pool (apart from local 'de novo' synthesis) and uses these for heat production and replenishment of its own cellular stores.

Finally, cold exposure not only affects our energy, glucose and lipid metabolism but is also known to promote vasoconstriction in the peripheral arteries to prevent heat loss. Cold acclimation can positively affect our capacity for vasomotion of the distal parts of our body, which causes changes in the blood pool distribution, thereby affecting our cardiovascular system. Caution has to be taken with respect to cold exposure in un-acclimatized elderly since mild cold can substantially increase systolic blood pressure in both young adults and elderly (30). In the elderly, blood pressure remains elevated over a longer period of time (46). The effects of cold and variable ambient temperatures on our cardiovascular system are currently under investigation.

Heat

Not only cold but also exposure to heat can affect human energy metabolism, although the results are less evident and the upper critical temperature of thermoneutral zone has not been studied in detail in humans. Physiological reactions to cold are generally focused on increasing heat production to defend a drop of core temperature, whereas effective heat loss is the central goal when the body is exposed to heat. Here, thermoregulatory processes such as vasodilation and sweat production are of great importance.

Similar to the available literature regarding cold, also studies on acute heat exposure and heat acclimation mainly focus on extreme conditions, which may not reflect the thermal conditions we normally experience in everyday life. Most heat exposure and heat acclimation studies generally employ high temperatures combined with exercise (so-called active heat acclimation), to yield important implications for target groups such as athletes and the military. Results of these studies show that high ambient temperature in combination with high metabolic rate (exercise) leads to significant (thermo-)physiological adaptations, e.g. improved cardiovascular function and cutaneous vasomotor function, reduced core body temperature (CBT) and more efficient sweating (47).

In contrast to the numerous studies on active heat acclimation, only few studies evaluated passive acclimatization to heat, without the additional effect of raised endogenous heat production (48–53). Results of passive heat acclimation studies also show significant reductions of CBT, sweating and cardiovascular function, similar to those effects observed after active heat acclimation in humans. Importantly, even though the heat stimulus was provided in a passive manner, the few studies available in the literature employed very high air temperatures ranging from 45°C to 55°C, which do not realistically reflect everyday living circumstances.

It is, however, of particular interest to study more mild but realistic everyday (heat) conditions with respect to their effect on human metabolism and health, as they are hardly if at all represented in the current literature, but have a great practical importance. Therefore, we studied the effect of *passive mild* heat acclimation on thermophysiology and cardiovascular health in humans. No increase in thermogenesis during heat exposure was observed. Interestingly, although in a first study in healthy lean men, we show that *passive mild* heat acclimation induces distinct thermophysiological adaptations, such as a decrease of CBT, a redistribution of skin temperature towards warmer distal and cooler proximal parts, decreased sweating and lowered blood pressure (54). This shows that even *passive* exposure to *mild* heat leads to physiological adaptation processes, which increase the resilience to heat. The decrease of blood pressure furthermore suggests that also cardiovascular health might be positively affected by repeated exposure to heat, which likewise has been earlier indicated in other studies (55,56).

Interestingly, similar to acute cold exposure and cold acclimation, also heat has been shown to affect glucose metabolism. Already in 1999, a study by Hooper (57) showed that glucose handling improved significantly in T2DM patients after daily hot baths over the course of 3 weeks. Moreover, literature has previously suggested an improvement of diabetes status (based on HbA1c, glycosated haemoglobin) in the warmer months of the year (58–62). In order to test the effect of passive mild heat acclimation on glucose metabolism, we set up another study in elderly men with obesity. Results suggest that 10 d of passive mild heat acclimation in elderly participants with obesity induced thermophysiological and cardiovascular adaptations just as in the healthy population but also seem beneficially affected glucose metabolism (analysis of the data is in progress).

Besides physiological adaptations, mild heat exposure may exert psychological or behavioural effects. Another very important but frequently overlooked aspect of thermoregulation is, indeed, the *conscious behavioural* regulation of body temperature. We showed that passive mild heat acclimation lead to better acceptation of warm thermal environments and the initiation of behavioural thermoregulation at higher mean skin temperatures (63).

Taking all this information into account, the importance of temperature as a lifestyle factor is highlighted. In future, the interaction of temperature, occupant physiology and health should be considered for the design and development of thermal indoor environments.

Light

Just as temperature, also light conditions can affect our health and well-being (64,65). Most well known is the

application of light in winter time to treat seasonal affective disorder (66). A reason for the impact of light is that it is the strongest timing cue for the circadian clock (67). The natural day–night rhythm of light synchronizes the circadian rhythm to the 24-h day. In the evening, the natural rise of melatonin secretion prepares the body and metabolism for sleep at night (68). Due to the modern living patterns in which people spent the majority of their time indoors, the natural sleep/wake rhythm is influenced by artificial light exposure rather than by the natural day–night rhythm. As a consequence, people are exposed to light up to the late hours, with light intensities much lower during the day and many times higher in the evening (69). These circadian effects of light exposure are largely mediated by the intrinsic photosensitive retinal ganglion cells, which are most sensitive for light around 480 nm (blueish light) (70). Therefore, the spectral composition of the light also plays an important role in synchronizing the circadian rhythm (71). Disruption of the internal biological clock leads to lower vitality and alertness during the day and a decrease of both the duration and quality of sleep, (69,72) being crucial for health and well-being. In turn, correct light conditions have vitalizing alertness and performance-enhancing effects (73,74). Recent studies also show the importance of sleep quality (both duration and timing) and appropriately synchronized circadian rhythms on neurological and cardiometabolic health (75).

Interestingly, human energy metabolism is also influenced by the effects of light on our circadian rhythm. Indeed, light conditions affect the body's energy metabolism; the timing of light is positively correlated with a significant increase in overweight (76) and light treatment may be effective for related diseases such as T2DM (77). In contrast, a mismatch between the internal biological clock and the behavioural (social) clock is related to an increased body mass index (78). Sleep–wake cycle irregularities are more common in people with T2DM (79), and being a later chronotype is associated with poorer glucose control in T2DM patients (80). Taken together, these studies indicate that a late timing of sleep is associated with overweight and related diseases. Furthermore, observations indicate that light exposure at night is associated with obesity, diabetes and increased plasma lipids (81,82).

Light and thermal physiology

From the earlier information, we can conclude that both ambient temperature and light exposure affect human thermophysiological responses. For instance, light intensity during the day under free-living conditions is correlated with the rhythmicity of wrist temperature, which is a non-invasive marker of the biological clock (83). Another marker of the biological clock, CBT, is lower during the night after a few hours of bright light during the day, indicating that the effect of light can have an influence several hours later (84).

Additionally, various experiments have shown that light and environmental temperature influence (thermo-)physiology and psychology and that these effects interact (for a review, see Te Kulve *et al*. (85)). Experiments performed in the evening show that light can delay the natural decline in CBT, proximal skin temperature and the natural increase in the distal to proximal temperature gradient (distal minus proximal skin temperatures), alongside with reduced sleepiness (86). So far, little is known about the effects of light intensity on thermophysiology at different times of day and its relation to alertness. Thus, it remains unknown how light history, timing, duration, intensity and spectrum of a light exposure impact thermophysiology (85).

A few studies indicate that bright light exposure in the morning decreases the CBT (87,88); however, for instance, Ruger *et al*. found no effect of afternoon bright light on CBT, but they did show that bright light reduced sleepiness (89). We recently showed in a tightly controlled laboratory study that morning light intensity (bright vs dim) and room temperature (three conditions: cool, thermoneutral or warm) independently affected body temperatures and alertness (90). In agreement with nocturnal studies, morning bright light reduced self-assessed sleepiness as compared to dim light. Interestingly, the bright light responses on body temperature in the morning were opposite compared to those reported during the evening and night. CBT and the proximal skin temperature were lower and the distal to proximal skin temperature gradient was higher when exposed to bright light. These results demonstrate that the effect of light on thermophysiological parameters depend on the time of the day and on the circadian phase. No significant effects on energy expenditure were found, but since body temperatures were changed by light conditions, it can be concluded that on the longer term, energy metabolism may be affected.

The spectral distribution of light can also influence body temperature and comfort experience (91). Few studies indeed report that light colour (correlated colour temperature [CCT]) affects CBT (92). CBT may be increased by blue light, and it might thereby enhance alertness. We recently showed that CCT and ambient temperature independently affected the CBT and furthermore (during a temperature intervention) that body temperature distribution was related to sleepiness and reaction time (91). Although many questions still remain, it can be concluded that both light intensity and CCT affect thermophysiological parameters. Acute effects of light on energy expenditure are not found, but there might be reason to speculate that long-term effects may be significant. This is subject to further investigation.

The interaction between the effects of light on ambient temperature also features another interesting (psychological) aspect: generally, red light is perceived as warmer, and

indeed several studies indicate that the ambient temperature is judged differently depending on the spectrum of the light conditions (e.g. Albers *et al*. and Huebner *et al*. (93,94)). Recently, we found that visual comfort and thermal comfort are related (95). This means that by manipulating light conditions, subjective thermal comfort and sensation of the ambient condition can be affected. Slightly (healthy) cool and warm conditions can be manipulated to be more acceptable using the right light conditions in terms of timing, intensity and colour. In future studies, the interactions of these two environmental conditions (temperature and light) deserve more attention.

Conclusion

Recent studies indicate positive effects of the environmental factors heat, cold and also light on metabolic health. Although effects on energy metabolism, glucose and lipid metabolism are evident, the effect size clearly depends on the quantity and quality of the factors involved: actual temperature, brightness of the light, CCT, timing and the duration of the exposure (acute exposure vs acclimation). To be able to apply this knowledge in practice, more practical information on the temperature variation (how much, during which times of the day) is needed. It is furthermore necessary to translate results from laboratory studies (both with respect to light and temperature) to real world situations. Therefore, the newly gained insights need to be tested in real life living lab situations. Also, the interactions between light and ambient temperature should be further investigated.

A very important matter are, moreover, the long-term effects of environmental factors on human health. On the one hand, it should be evaluated how long effects remain (for instance, after cold acclimation) and on the other hand, how big the actual impact of those long-term effects is on our metabolic health. In any case, with the current knowledge available, the design of our indoor climates should no longer be based on comfort or traditional habits only. With modern technology, a much healthier indoor environment can be established.

Conflict of interest statement

No conflict of interest was declared.

Acknowledgements

This project has received funding from the EU FP7 project DIABAT under grant HEALTH-F2-2011-278373; Organization for Scientific Research (NWO) under grant TOP 91209037; TKI Energo and TKI Solar Energy project TRECO under grant TEGBj13023; the Dutch TKI Urban Energy (TEUE117001); and STW – Philips Electronics Nederland B.V. Partnership Program, no. 12733.

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