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Cold exposure – an approach to increasing energy expenditure in humans

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A little cold a day keeps the doctor away

Obesity is a consequence of positive energy balance, which can be counterbalanced by eating less, increasing physical activity, or pharmacological approaches. However, weight maintenance is generally disappointing, and long-term use of pharmaceuticals has been limited because of lack of efficacy, poor long-term adherence rates, and serious adverse effects. These limitations indicate that, given our current knowledge and available technologies, insights from other fields of research will be necessary to permit exploration of new ideas and develop effective applications. We suggest that regular exposure to mild cold may provide a healthy and sustainable alternative strategy for increasing energy expenditure.

Obesogenic thermal environment

In the past century several dramatic changes in the daily living circumstances in Western civilization have occurred, affecting health. For example, we are much better able to control our ambient temperature. Consequently, we cool and heat our dwellings for maximal comfort while minimizing our body energy expenditure necessary to control body temperature.

Although people are generally becoming older, and many life-threatening diseases have decreased in prevalence, other diseases and syndromes have increased immensely. Most eye-catching are overweight and obesity, now affecting over 500 million people (http://www.who.int). Obesity increases the risk of developing type 2 diabetes (T2D), cardiovascular diseases (CVD), and some forms of cancer.

Obesity is linked not only to excessive food intake (energy intake) but also to physical inactivity (reduced energy expenditure). In the past two decades major scientific and financial interests have focused on counteracting excessive energy intake to tackle 'diabesity'. This approach now appears to be rather disappointing in terms of Public Health and, until now, effective treatment strategies against obesity and T2D are still lacking. This holds true, with respect to long-term effects on weight loss and weight maintenance, for both lifestyle intervention programs and pharmacological therapies. Because 90% of the time we are exposed to indoor conditions, health aspects of ambient temperatures warrant exploration. What would it mean if we let our bodies work again to control body temperature? It is hypothesized in this paper that the thermal environment affects human health – and more specifically that frequent exposure to mild cold can affect our energy expenditure significantly over sustained time-periods.

Cold exposure

It is well known that people shiver in response to cold. By shivering, heat production (a synonym for energy expenditure and thermogenesis) can increase to a level fivefold above the resting metabolic rate [1]. Shivering thermogenesis (ST) therefore is important for short-term protection against hypothermia, but is uncomfortable and impedes coordinated movements. Alternatively, studies in rodents have shown that nonshivering thermogenesis (NST) (see Glossary) can replace ST by activating brown adipose tissue (BAT) [2]. Although NST had been reported in

Glossary

Acclimation: the process in which an individual adjusts to a gradual experimentally induced change in its environment.
Acclimatization: the process in which an individual adjusts to a gradual naturally induced change in its environment.
Adipostat hypothesis: the hypothesis proposes that changes in body weight should be compensated by changes in food intake and thermogenesis, thus increased thermogenesis would result in increased food intake.
Arrhenius law (Q_{10} effect): a formula for the temperature dependence of reaction rates. According to the Arrhenius law, for common chemical reactions at room temperature, the reaction rate doubles for every 10 °C increase in temperature.
Basal metabolic rate (BMR): the amount of energy expended at rest in a thermal neutral environment while in the post-absorptive state.
Convective heat loss: heat loss by the movement of a fluid medium.
Nonshivering thermogenesis (NST): a cold-induced increase in heat production not associated with the muscle activity of shivering. It occurs in BAT and is mainly regulated by thyroid hormone and the sympathetic nervous system.
Radiative heat loss: heat loss due to emission of electromagnetic waves.
Thermoneutral zone (TNZ): the range of ambient temperatures that do not induce regulatory changes in metabolic heat production or evaporative heat loss. Energy expenditure is at basal level.
Thermal comfort zone (TCZ): the range of ambient temperatures, associated with specified mean radiant temperature, humidity, and air movement, within which a human in specified clothing expresses satisfaction with his thermal environment.

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humans earlier, the relationship to functional BAT in adult humans was not shown until 2009 (among others, [3,4]).

Human NST shows high individual variation. Some young adults and most elderly people show decreased NST in response to mild cold; this has been attributed to reduced metabolism in the tissues of the cooled extremities, which may be explained by Arrhenius law (Q_{10} effect) [5]. However, in most young and middle-aged people NST increases by between a few percent and 30% in response to mild cold exposure. Thus, NST can have a physiologically significant effect upon energy expenditure and can potentially affect our energy balance. With respect to the physiological basis of NST, several studies have shown that there is a significant relationship between BAT content and the level of cold-induced thermogenesis [6] (for an overview on potential pathways and mechanisms to activate BAT, see [7]). However, the actual contribution of BAT to NST still awaits elucidation. Some studies indicate a contribution of skeletal muscle to NST, but the results of different studies are conflicting [6]. Notwithstanding the contributions of the tissues involved, whole-body calorimetry clearly shows that NST can be a significant contributor to total energy expenditure.

Cold acclimatization

In 1961 Davis *et al.* showed that, paralleling rodent studies, humans are able to increase nonshivering thermogenesis upon regular cold exposure [8]. Recent cold acclimation studies have revealed comparable results and a concomitant increase in BAT activity, with NST being related to BAT activity [6,9]. Yoneshiro *et al.* also found a significant decrease in body fat content following a 6 week (2 h/day at 17 °C) cold acclimation protocol [9]. Interestingly, we observed that shivering and thermal discomfort decreased during a 10 day cold acclimation protocol (6 h exposure to 15 °C/day) [6]. It is obvious that 15 °C is too low for practical application in the built environment, but we expect that mild cold (e.g., 18–19 °C) will also result in increases in NST and BAT, and with acceptable thermal comfort levels. However, the time needed will be longer and the final level of adaptation will relate to the intensity, duration, and timing of cold exposure.

In fact, this takes place to some extent in daily life as a function of the seasons. The Netherlands, for example, are characterized by a mild temperate climate with relatively cool summers and mild winters. Even though these seasonal variations in outdoor temperature are relatively small, and most people live inside all day long, laboratory tests show that winter NST is significantly larger compared to summer, in the same volunteers [10].

One could argue that other changes will compensate for the increased energy expenditure. Indeed, according to the adipostat hypothesis, changes in food intake will compensate for alterations in energy expenditure and body weight. However, there is evidence that increased food intake does not fully compensate for cold-induced NST, and therefore may counteract obesity [11].

Similarly to exercise training, we advocate temperature training. When we do not engage in daily exercise we lose the capacity to perform physically and may become more vulnerable to developing obesity and CVD. Therefore, people are nowadays advised to train regularly. By contrast, with respect to temperature, we offer so-called thermally 'comfortable' environments. In fact, indoor temperatures in most buildings are regulated to minimize the percentage of people who are dissatisfied – the so-called predicted mean vote (PMV) model [12]. This results in relatively high indoor temperatures in wintertime. This is evident in offices and in dwellings, and is most pronounced in care centers and hospitals. By lack of exposure to a varied ambient temperature, entire populations may be prone to developing diseases such as obesity. In addition, people become vulnerable to sudden changes in ambient temperature. Epidemiological studies indeed indicate associations between periods of cold weather and mortality from CVD, pulmonary disease, or cancer [13]. Cold spells affect the elderly who, apart from biological aging effects on thermoregulation, show a deterioration of thermal responses. As a result they become more vulnerable during cold spells and heatwaves, and show an increased likelihood of becoming obese.

Therefore, in parallel to physical exercise, one should promote temperature training as part of a healthy lifestyle.

Thermoneutral zone (TNZ) and thermal comfort zone (TCZ)

Physiologists have defined the TNZ as the range of ambient temperatures at which temperature regulation is achieved solely by control of (convective and radiative) heat loss – in other words, without regulatory changes in metabolic heat production or evaporative heat loss (sweating) (Figure 1). As mentioned above, people can tolerate and even judge temperatures comfortably, even if they are below the lower bound of the TNZ, which means that people still feel comfortable although the body spends more energy in keeping body temperature stable. It therefore seems that

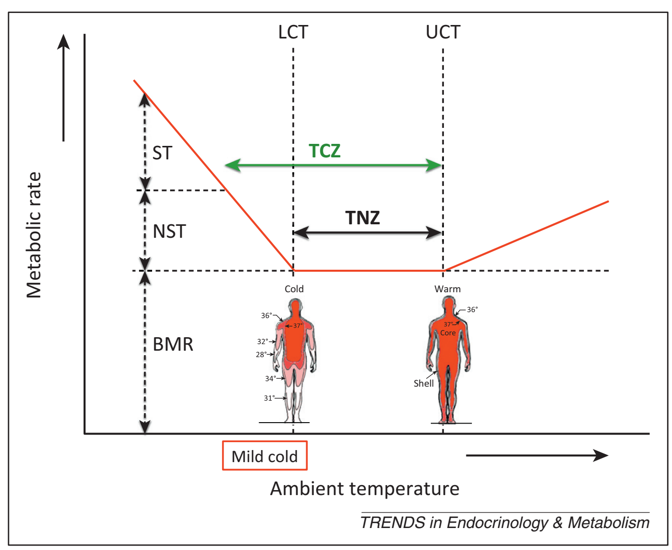

Figure 1. Thermoneutral zone (TNZ) and thermal comfort zone (TCZ). The TNZ is the ambient temperature range in which energy expenditure is at basal level (basal metabolic rate, BMR) and heat dissipation by the body is achieved by changes in peripheral perfusion. Below the lower critical temperature (LCT), nonshivering thermogenesis (NST) and eventually shivering thermogenesis (ST) take place. Above the upper critical temperature (UCT) increases in energy expenditure also occur, partly due to an increase in heart rate. An important question is how the TCZ is related to the TNZ. The expected TCZ after acclimation is depicted. For clarity the sweat response in not indicated.

the TCZ may be larger than the TNZ, and may further increase with the level of acclimatization (Figure 1).

The ambient conditions in the built environment are designed to accommodate thermal comfort criteria based on the PMV model [12]. This results in uniform indoor air temperatures, with minimal variations according to time of day or season. This applies for all building types regardless of climate, season, or daily outdoor temperature variation. In addition to the described negative impact upon our health, this leads to high energy consumption by buildings.

More recent adaptive models recognize that humans tolerate and adapt to different thermal environmental conditions depending on outdoor environmental conditions [14]. Indeed, in both young adults and the elderly, gradual temperature variations of ± 2 °C/h over the range 17–25 °C are accepted without significant discomfort [15]. Application of an adaptive comfort model results in a (seasonally) more varied indoor thermal climate compared to the PMV model, and leads to improved comfort, provided that the occupants have the ability to influence their own thermal environment. During winter, this means that the indoor temperature can be lower, both temporally and spatially, such that occupants are regularly exposed to cool conditions, thereby increasing their energy expenditure.

Conclusion

Maximal thermal comfort in the built environment may increase our susceptibility to obesity and related disorders, and in parallel requires high energy use in buildings. Mild cold exposure increases body energy expenditure without shivering and without compromising our precious comfort. Hence, rethinking our indoor climate by allowing ambient temperatures to drift may protect both health and bank account.

Current research aims to pinpoint the physiological basis for NST so as to benefit optimally from its potential. For instance, the recent rediscovery of functional BAT in humans, together with a sharp rise in our understanding of the underlying cellular mechanisms, has provided routes for pharmacological intervention. However, letting our body spend more energy to maintain thermal balance may positively affect health on a population scale. Furthermore, temperature training by regular exposure to mild cold keeps the peripheral vascular system in motion (e.g., vasoconstriction during cold and vasodilation during heat), and thereby helps to train the cardiovascular system. The effect of mild cold acclimatization on the immune system needs attention; the limited data available do not show impairment of the human immune system. At older ages, sudden cold exposure can have serious effects on systemic parameters such as blood pressure and core temperature. Nevertheless, cold-acclimatized individuals are less vulnerable to such sudden exposures, and temperature training may therefore contribute to a healthy aging strategy. Last but not least, allowing indoor temperatures to drift more than permitted under current standards can substantially reduce energy consumption by the built environment.

More frequent cold exposure alone will not save the world, but is a serious factor to consider in creating a sustainable environment together with a healthy lifestyle.

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References

1 Jansky, L. (1998) Shivering. In *Physiology and Pathophysiology of Temperature Regulation* (Blattheis, C.M., ed.), World Scientific
2 Cannon, B. and Nedergaard, J. (2004) Brown adipose tissue: function and physiological significance. *Physiol. Rev.* 84, 277–359
3 van Marken Lichtenbelt, W.D. *et al.* (2009) Cold-activated brown adipose tissue in healthy adult men. *N. Engl. J. Med.* 360, 1500–1508
4 Virtanen, K.A. *et al.* (2009) Functional brown adipose tissue in healthy adults. *N. Engl. J. Med.* 360, 1518–1525
5 Kingma, B.R. *et al.* (2011) Increased systolic blood pressure after mild cold and rewarming: relation to cold-induced thermogenesis and age. *Acta Physiol.* 203, 419–427
6 van der Lans, A.A. *et al.* (2013) Cold acclimation recruits human brown fat and increases nonshivering thermogenesis. *J. Clin. Invest.* 123, 3395–3403
7 Harms, M. and Seale, P. (2013) Brown and beige fat: development, function and therapeutic potential. *Nat. Med.* 19, 1252–1263
8 Davis, T.R.A. (1961) Chamber cold acclimatization in man. *J. Appl. Physiol.* 16, 1011–1015
9 Yoneshiro, T. *et al.* (2013) Recruited brown adipose tissue as an antiobesity agent in humans. *J. Clin. Invest.* 123, 3404–3408
10 van Ooijen, A.M.J. *et al.* (2004) Seasonal changes in metabolic and temperature responses to cold air in humans. *Physiol. Behav.* 82, 545–553
11 Cannon, B. and Nedergaard, J. (2009) Thermogenesis challenges the adipostat hypothesis for body-weight control. *Proc. Nutr. Soc.* 68, 401–407
12 Fanger, P.O. (1970) *Thermal Comfort*, Danish Technical University
13 Gomez-Acebo, I. *et al.* (2013) Cold-related mortality due to cardiovascular diseases, respiratory diseases and cancer: a case–crossover study. *Public Health* 127, 252–258
14 de Dear, R.J. and Brager, G.S. (1998) Developing an adaptive model of thermal comfort and preference. *ASHRAE Trans.* 104, 145–167
15 Schellen, L. *et al.* (2010) Differences between young adults and elderly in thermal comfort, productivity, and thermal physiology in response to a moderate temperature drift and a steady-state condition. *Indoor air* 20, 273–283