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Cold-induced thermogenesis in humans

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Abstract

A basic property of endothermic thermoregulation is the ability to generate heat by increasing metabolism in response to cold ambient temperatures to maintain a stable core body temperature. This process, known as cold-induced thermogenesis (CIT), has been measured in humans as early as 1780 by Antoine Lavoisier, but has found renewed interest because of the recent 'rediscovery' of thermogenic, cold-activated brown adipose tissue (BAT) in adult humans. In this review, we summarize some of the key findings of the work involving CIT over the past two centuries and highlight some of the seminal studies focused on this topic. There has been a substantial range of variability in the reported CIT in these studies, from 0 to 280% above basal metabolism. We identify and discuss several potential sources of this variability, including both methodological (measurement device, cold exposure temperature and duration) and biological (age and body composition of subject population) discrepancies. These factors should be considered when measuring CIT going forward to better assess whether BAT or other thermogenic organs are viable targets to combat chronic positive energy balance based on their relative capacities to elevate human metabolism.

INTRODUCTION

The balance between energy expenditure (EE) and energy intake ultimately determines body weight. Resting EE is the major component (50–80%) of total daily EE in an adult human.[1] Thus, even small changes in resting EE, if not compensated by changes in food intake, can have long-term effects on body weight.

Resting EE can also adapt to changes in environmental temperature. In colder temperatures, resting EE increases to help maintain a stable core body temperature, serving as a source of heat production to counterbalance heat loss. This adaptive component of resting EE is defined as cold-induced thermogenesis (CIT). In small mammals (e.g., mice), CIT-based heat production is critical to maintain consistent core body temperature because their relatively high surface-area-to-volume ratio results in increased avenues for heat loss in the cold. Consequently, these animals can have large amounts of the cold-activated, thermogenic

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CONFLICT OF INTEREST

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organ known as brown adipose tissue (BAT) and can increase their metabolic rate up to 4–5 times the thermoneutral resting EE at temperatures near 4 °C.[2–4] In contrast, adult humans have a much lower surface-to-volume ratio and are thought to be much less reliant on CIT to maintain body temperature. Currently, we are uncertain of the magnitude of maximal human CIT and how we can safely harness it to help us combat obesity.

The aim of this review is to briefly summarize some of the previous work on CIT measurement in humans, from the earliest measurements by Lavoisier, Voit, Swift, Hardy and Winslow to the modern-day measurements primarily targeted at understanding the contribution of adult human BAT to CIT. We attempt to identify potential sources of experimental variability, such as differences in measurement devices, subject population (sex, age and body composition), degree and duration of cold exposure, clothing level and exposure medium (air, water immersion or perfused suits and blankets). Understanding these differences may inform future experimental design to further explore the physiology of human thermoregulation and CIT.

THERMAL BIOLOGY OF CIT USING ANIMAL DATA AND MODELS

Many pioneers in the study of metabolism, including Lavoisier and Laplace (1780), Rubner (1902), Krogh (1918), Kleiber (1927), Benedict and Fox (1933), Swift and Forbes (1939) and Scholander *et al.* (1950), studied CIT produced by animals of various sizes and regions while gradually lowering air temperature.[5] Although there have been some more recent refinements surrounding inter- and intraspecies variations in the CIT response (for instance, see Fristoe *et al.*[6] or Fischer *et al.*[7]), the collective results of these researchers demonstrate that the framework of endothermic thermoregulation can be described by the fundamental principles of thermodynamics, that is, Newton's law of cooling and Fourier's law of heat flow.[5] In accordance with these principles, endothermic animals are able to maintain a consistent body temperature in response to changing ambient temperatures by either altering heat conductance through physiological adaptations, such as vasoconstriction and piloerection, to reduce heat loss from the body surface or by increasing heat production (EE). The temperature range at which conductance altering mechanisms alone are sufficient to maintain a minimal and consistent level of heat production to balance heat loss is called the thermal neutral zone. This minimal EE within the thermal neutral zone is known as the basal metabolic rate (BMR). In ambient temperatures below a lower critical temperature (T_{lc}), these responses cannot sufficiently compensate for the increased heat loss and additional EE (i.e., CIT) is needed to prevent core body temperature from falling. As shown in Figure 1, the gradual increase in CIT with decreasing ambient temperatures reflects the effort to maintain net heat balance in the animal. Interspecies differences in insulation level (fur or hair), body size and physiology result in variations in the thermoneutral ambient temperature range, the basal metabolic rate and the rate of the CIT increase.[6,8]

CIT RESPONSE IN HUMANS

As early as 1780, physiologists have applied the methodologies of direct and indirect calorimetry to measure CIT in humans (Table 1).

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Lusk[9] highlighted the earliest known work by Lavoisier who discovered that a resting man absorbed 17% more oxygen at 12 °C than at 26 °C, although the details of the study are not well documented. Nearly a century later, Voit[10] carefully described a series of experiments measuring the carbon dioxide (CO_2) production of a healthy male volunteer (71 kg) in temperatures ranging from warm (30 °C) to cold (4.4 °C) in the Pettenkofer respiration chamber (or as he called it the 'big Pettenkofer Respiration box'). The measurements took place on different days during a German winter (between 27 January and 24 February 1876), and the 'dedicated' subject entered at 1100 hours under fasted condition and sat in an armchair without movement (resting EE) for 6 h. The results showed that the CO_2 production did not vary significantly at ambient temperatures above 16.2 °C, but increased by up to 36% in the cold, which could not be explained by movement (Figure 2).

Swift[11,12] tried to quantify the role of shivering in CIT by studying 21 young subjects in a 2 °C refrigerator for 75 min. He found that in the absence of shivering, the cold condition increased heat production by ~ 11% compared with the warm basal condition (23–25 °C). However, when intense shivering occurred, the metabolism increased to ~ 400% of the BMR.

In perhaps the most classical study, Hardy and Dubois[13] measured two healthy subjects (themselves) in a direct calorimetry chamber by determining the three components of heat loss: radiative, conductive/convective and evaporative under strictly controlled conditions (naked, fasted, supine, motionless and awake) for 2–3 h/day during which the air temperature was set from 22.5 to 35 °C (Figure 3). A U-shaped curve was observed in heat loss vs environmental temperature, from which they observed a minimal zone of net heat loss (similar to thermal neutral zone) of 29–33 °C. The detailed body temperature measurements collected in this study demonstrated that, while skin temperatures fell during cold exposure, decreasing much more markedly in peripheral locations compared with the central skin sites, the core (rectal) temperature was highly conserved (< 1 °C change) throughout the tested ambient temperature range. Interestingly, heat production (EE), measured using oxygen consumption and CO_2 production, showed little to no change over this temperature range in these two male subjects, despite reports that shivering became uncontrollable during some of the extreme cold conditions.

Winslow *et al.*[14] studied one 'slender' and one 'stout' healthy volunteer in a wider environmental air temperature range (6.8–35.5 °C), and found similar U-shaped curves for heat loss as Hardy and Dubois. They further observed that the slender subject experienced an increase in metabolism (CIT) only when his core temperature fell below 36 °C, but the variability appeared high. The stout subject maintained core temperature and had no CIT response.

In a follow-up to their 1937 study, Dubois *et al.*[15] used a similar experimental design and recorded serial metabolic measurements of 13 healthy young women (age 25.9 ± 6.1 years, body mass index 21.4 ± 2.8 mg/kg^2) in temperatures from 22 to 36 °C. The authors noted that 23 of the 32 measurements in the 'cold zone' (22–26.9 °C) resulted in increased metabolism compared with the 'comfort zone', presumably between 27–32 °C, which was deemed statistically significant. However, the average 'cold zone' increase was small and the

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'the causes [were] still uncertain'. Great individual variability was also observed in these studies, with some subjects (60%) showing robust CIT and hot-induced thermogenesis while others exhibiting no discernible change in metabolism. According to the authors, the CIT was 'greater than the amount that could be ascribed to muscle tension or restlessness'.

A subsequent study by Buskirk *et al.*[16] used indirect calorimetry to measure the CIT of four fasted, healthy, lean, young male volunteers for ~ 3 h in more extreme temperature conditions (26.6 °C vs 10.0 °C). They reported a much more marked increase in metabolism of 55% (32–91%), but noted that this included both body motion and shivering.

Using whole-room indirect calorimetry chambers (respiration, metabolic), more recent studies have recorded variable, but generally more modest, magnitudes of CIT (3–7%) when ambient air temperature ranges are close to normal indoor living conditions (Table 1). Other investigators used indirect calorimetry (metabolic) carts and other exposure media (e.g. water-immersion or water-perfused suits) for CIT measurements over shorter periods and have yielded relatively higher magnitudes (10–280%, Table 2).

THE POTENTIAL CAUSES FOR THE WIDE VARIABILITY OF CIT RESPONSE IN HUMANS

Although individual variability in the CIT is evident and noteworthy in almost all studies on this subject, there is also considerable interstudy variation as well (e.g. Tables 1 and 2). Both methodological and biological factors may be responsible for these discrepancies. In the following section, we consider several potential sources of this variability from both of these categories.

Method of metabolic measurement

Room calorimeters have been used for more than a century to measure heat loss directly and/or heat production indirectly (through oxygen consumption and carbon dioxide production) in an environment where ambient temperature can be tightly controlled. Early experiments tended to use direct+indirect calorimeters and measured heat loss and production simultaneously.[13,14] However, early calorimeters typically consisted of many custom-made components and required a team of trained operators to accomplish one experiment. This made experiments conducted with these devices quite complex, with high potential for noise, interdevice variation and operator error. Most current whole-room devices are exclusively indirect calorimeters and take advantage of modern, industrially produced gas analyzers to measure subject-generated changes in room air composition. Although these modern indirect calorimeters are incapable of directly assessing heat loss, their reported precision is 2–3% for ~ 24 h of measurement of EE at normal operating temperatures.[17] By performing a series of propane combustion experiments in ambient temperatures from 16–32 °C, we have validated that the accuracy of our three indirect room calorimeters (100.0 ± 1.0% EE recovered) is not affected by ambient temperature, provided that the temperature inside and surrounding the room calorimeter is stable. Indirect calorimetry (metabolic) carts have been as an alternative to room calorimeters for shorter duration assessments of CIT because of their wider availability. They have higher sensitivity

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than room calorimeters because of less dead-space volume. Measurements with these devices can also be performed in close proximity to the subject, allowing the operator to better observe and potentially minimize the effects of shivering and movement. Both of these attributes may be advantageous to detect small CIT responses. However, these devices increase subject burden and potential for discomfort and thus are not recommended for longer duration measurements. The acute nature of these measurements may not allow subjects to achieve a steady-state metabolism, and transient responses may increase intra- and intersubject variability. The impact of colder ambient temperatures on the validity of metabolic carts is also unknown.

Temperature range of cold and warm exposure

The range of temperatures used to assess human CIT represents another source of variability. As CIT is defined as the change in resting EE measured at cold and thermoneutral temperatures, its magnitude can be influenced by the temperatures chosen for both cold and baseline (i.e., thermoneutral) conditions. Although the lower critical temperature (T_{lc}) has not been rigorously determined in humans, based on currently available data it is generally thought to occur at ambient temperatures > 24°C and could vary between individuals. A baseline EE measured below the T_{lc} (perhaps 22 or 24 °C) could be higher than the true BMR which would result in a falsely low CIT response. Similarly, choosing a lower fixed cold temperature (e.g., 16 °C vs 22 °C) could influence the magnitude of observed CIT, particularly when only two temperature conditions are measured. Some researchers attempt to minimize the possibility of underestimating CIT by using a personalized cooling protocol in which the subject is gradually cooled to the level of overt shivering and then the temperature is slowly increased until shivering stops. The resultant temperature is said to be the lowest non-shivering temperature and is thought to maximize individual non-shivering thermogenesis. The fixed temperature method may be more suitable for comparing CIT responses in a homogeneous subject population exposed to standardized environmental condition, whereas the personalized approach may be favorable for comparing responses in heterogeneous populations or for longitudinal intervention studies that can alter cold tolerance.[18]

Cold exposure medium

Researchers have applied cold using a variety of different methods to study the human CIT response, including cold air exposure, water immersion, intravenous water infusion, various water-perfused garments and intermittent localized contact with ice blocks. The physical properties of these different media may contribute to the variability of CIT observed in the literature. For example, the thermal conductivity of water is nearly 25 times that of air, thus the rate of heat loss from the body is much greater in cold water compared with that in cold air of the same temperature.[19,20] One result of the difference in thermal conductivity is a shift in the reported thermoneutral zone temperatures for water immersion vs air cooling. In air, the T_{lc} is thought to be near 22–24 °C, but for water a T_{lc} of 31–33 °C is usually reported, with observable shivering commonly occurring below this temperature range.[19,21] The duration of the cold exposure in each medium may also have a role in reported CIT values. Time-dependent increases in CIT have been reported in some studies using both air-based[15,22] and water-based[19,21] cold exposure. However, these temporal trends in CIT and

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heat loss appear to follow Fourier's law of cooling, with more striking increases occurring in water,[19,21] because of its high thermal conductivity, and in colder temperatures.[15,19,21,22]

Shivering

Increasing voluntary movement can be an effective way to keep warm in cold temperatures as a result of the additional heat created by large groups of skeletal muscles contracting. However, physical activity is typically restricted in studies of CIT. On the other hand, it is difficult to eliminate the involuntary tensing of the muscles without motion (isometric contractions) which define shivering. Shivering is a common defense mechanism against cold that can sharply increase heat production, raising the metabolism up to five times the BMR at peak intensity.[23] Although voluntary movement can be observed and objectively measured, shivering and muscle tightening is much harder to quantify. Most studies of CIT attempt to measure the non-shivering component of cold thermogenesis by choosing temperatures that do not elicit visible or self-reported shivering. However, direct observation and subjective shiver reporting can be unreliable. Alternatively, electromyographic (EMG) techniques have been used to record objectively the electrical activity of muscles during shivering. In some cases, indwelling EMG sensors are placed via fine-wire needles directly into the muscle fibers of animals,[24] although newer surface-based EMG methods are much more practical and less invasive for human studies. Surface EMG, however, cannot measure the activity of deeper muscles that have been found to be active in cold (e.g., scalenes, psoas, Longus colli).[25] Moreover, to compare the activation level of different muscle groups within an individual or the shivering intensity of the same muscle group between individuals, EMG signals must be carefully normalized to either standardized resting, non-shivering conditions or maximal isometric voluntary contractions.[26]

Clothing level

Fur or fleece thickness in various animal species has been shown to have a marked influence on the CIT, with thicker fur (higher insulation) resulting in a lower T_{lc} and less marked CIT slope.[7,27] Differing amounts of permitted clothing or bedding represent an analogous source of insulation variability seen in studies of human CIT. The level of thermal insulation provided by various garments is commonly quantified in Clo, where zero Clo corresponds to a naked person and one Clo corresponds to a person wearing a typical business suit. Most participants in studies performed before the 1970s typically were naked or wore very limited clothing. However, such conditions are rarely deemed practical or ethical by current research standards. As such, clothing conditions may not always be strictly controlled (e.g., material and fit of clothes, and blankets/duvet may be used in some but not in all subjects). For example, Warwick *et al.*[28] allowed subjects to choose the level of daytime clothing and nighttime bedding they wore in both 28 °C and 20 °C. Not surprisingly, subjects chose to wear more clothing in the cold and while sleeping, which may have lead to a smaller and more variable CIT response (5.0 ± 5.5%). In another study, Claessens-van Ooijen *et al.*[29] used quite different experimental conditions to study the CIT response of lean and overweight men. In that study, participants wore standardized clothing of sweat shirts and pants (Clo = 0.71) and EE measurements were conducted in a 15 °C room for 1 h under what were designated as thermoneutral conditions (covered with a 0.68 Clo duvet) and during 1 h of mild cold exposure (duvet removed). While the authors observed a large CIT

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response in the lean subjects (17.2%), it is possible that subjects may not have reached steady-state metabolism in both conditions because of an unusual testing conditions and the short duration of the measurements.

Adiposity

Based largely on earlier studies of CIT in humans, higher body fat content is thought to provide increased insulation and have a blunting effect on CIT, similar to external insulators. The work Hardy and Dubious,[13] Winslow *et al.*[14] and Cannon and Keatinge[21] seem to lend support to this premise, although the number of overweight or obese participants was rather low in all cases (≤2 subjects). More recent studies comparing lean and overweight/obese CIT response have reported mixed results. In the previously mentioned study by Claessens-van Ooijen *et al.*,[29] overweight subjects showed a blunted CIT response to a 'mild cold' (15 °C air) for 60 min as compared with lean subjects (6.4% vs 17.2%, $P = 0.04$). However, longer duration studies have shown less striking differences (2.2% for lean vs 0% for obese subjects for >24 h at 22 °C and 16 °C)[30] and even opposite trends (13.7% for lean vs 17.2% for obese subjects for 1 h at 22 °C and 2 h at 16 °C)[31] in CIT. Recent data in mice demonstrated that the insulation level of obese animals, quantified as the inverse of the CIT slope, is similar to lean counterparts, suggesting that greater adiposity and more abundant external insulation (fur) may have differential influences on CIT.[7]

Cold tolerance and brown adipose tissue

Acclimation to cold via chronic cold exposure may also impact the CIT response. In an early landmark study, Davis[32] conducted weekly measurements of the CIT of 10 young men over 31 days in the summer months while they were being cold acclimatized by remaining sedentary in 12 °C room wearing only shorts for 8 h/ day. He found that the subjects' CIT response decreased monotonically for the first 21 days, from ~ 55 to ~ 25% above BMR, where it plateaued. At the same time, EMG-measured shivering also decreased substantially, decreasing ~ 80% from day 0 levels, but was never completely abolished. When the study was repeated with a separate group of six subjects in the winter months, the initial (day 0) CIT response was lower but plateaued at nearly the same level, which suggested to the authors that natural seasonal acclimatization can occur. This standardized cold acclimation protocol supported previous reports from less standardized field studies conducted in different populations during which metabolic adaptation and shiver reduction occurred following repeated exposure to cold outdoor temperatures.[33–35] These early studies demonstrated that cold metabolic acclimation was possible but, as noted by Davis,[32] the mechanism for these changes remained unclear.

With the recent 'rediscovery' of BAT in adult humans via positron emission tomography-computed tomography scanning,[36–39] interest has been building about its metabolic potential, its role in CIT and its contribution to cold acclimatization in humans. Initial cross-sectional association studies between CIT and human BAT demonstrated mixed results. Several investigators have identified a correlation between CIT and BAT volume or activity,[40,41] while others provided evidence that skeletal muscle is more predominant in CIT.[42,43] Currently, we cannot definitively delineate the relative contributions of BAT and skeletal muscle to whole-body human CIT because of the challenges of measuring their separate

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metabolic activity *in vivo*.[18,44] However, several more recent studies with longitudinal designs have shown that BAT accumulates, and CIT measured during non-shivering cold challenges tends to increase following cold acclimatization.[25,45–49] Lee *et al*.[47] showed a small increase of BAT abundance in young men following 1 month of mild cold sleeping conditions (19 °C, hospital scrubs and sheet, ~ 8 h/day), but this was not accompanied by a change in CIT during a 24 h stay in a warm and cold respiration chamber. Using a lower temperature (17 °C wearing light clothing) but shorter daily exposure (2 h/day), Yoneshiro *et al*.[49] saw a positively correlated increase in BAT activity (58% increase from week 0) and CIT of a mild cold challenge (19 °C, 268% increase from week 0) after 6 weeks of acclimation. Similarly, van der Lans *et al*.[48] also showed a related, but less substantial increase in BAT(17% from week 0) and CIT (7% from week 0) using a shorter duration acclimation (10 days) with longer daily bouts of cold exposure (15–16 °C, 6 h/day wearing T-shirt and shorts) and a cold challenge involving the previously described personalized, maximal non-shivering cooling protocol. Using this cold acclimation protocol and CIT-testing procedure, the authors observed similar trends in BAT and CIT in obese participants[46] and subject with type 2 diabetes.[45] These studies suggest that both BAT activity and CIT are modifiable and may both be influenced by the degree and duration of repeated cold exposure. It is worth noting that while the daily exposures of these studies were less severe than those of the Davis study, the cold-challenge temperatures were warmer and not meant to elicit shivering, which may have contributed to their differential results in the CIT pattern before and after cold acclimation.

Age

Although older subjects have been shown to have reduced BAT volume in cross-sectional analyses,[36,50] to our knowledge, there is limited CIT data comparing young vs old subjects using air cooling. Using a 30- min 4 °C saline intravenous infusion method of cooling, Frank *et al*.[51] showed that older men (mean of 63 years) had a severely blunted thermoregulatory responses as compared with younger men (mean age of 21 years), including lower oxygen consumption rates (5.9 ± 0.6 vs 8.1 ± 0.5 ml/kg lean body mass/min, $P = 0.05$), reduced vasoconstriction and plasma norepinephrine responses. Core temperature also decreased more significantly in older vs younger subjects ($P = 0.001$).

SUMMARY

The recent interests in the area of CIT stem from its potential as a target for obesity prevention or treatment. We conducted a non-exhaustive review of 40+ clinical studies that primarily focused on the metabolic response to mild cold, to minimize the stress of overt shivering, CIT responses ranged from 0% to up to 90% above the 'warm' baseline levels. In general, being exposed to colder temperatures, over longer durations, in water (as opposed to air), wearing less clothing, and being younger, leaner and more cold acclimated can result in a higher relative CIT response. Studies using metabolic carts to measure cold-induced changes in metabolism over shorter durations tend to identify higher CIT responses compared with those using room calorimeters to measure more than 12 h. This trend may be the result of the metabolic cart capturing larger, transient increases in CIT that would remit if given more time or from confounding factors of the near-free-living conditions of the

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metabolic chamber such as physical activity, sleep and thermic effect of food. Less stringent thermal neutral conditions at baseline and individualized cooling protocols can also impact the variability in CIT responses across subjects. Shivering, although difficult to quantify, can also have a critical role in CIT. Moreover, most clinical research in this area has been performed on young, healthy, lean subjects, and on men more often than on women. Typically, very few subjects and very few temperature points (generally one warm and one cold) are measured per study. Thus, despite more than two centuries of effort to understand the mechanisms of CIT, we are still somewhat 'left out in the cold'.

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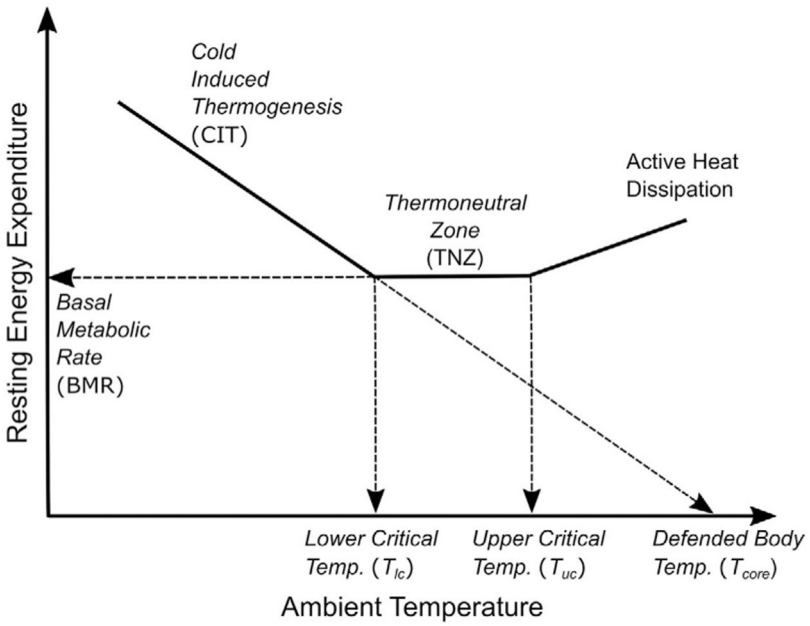

Figure 1.
Conceptual schematic of endothermic thermoregulation.

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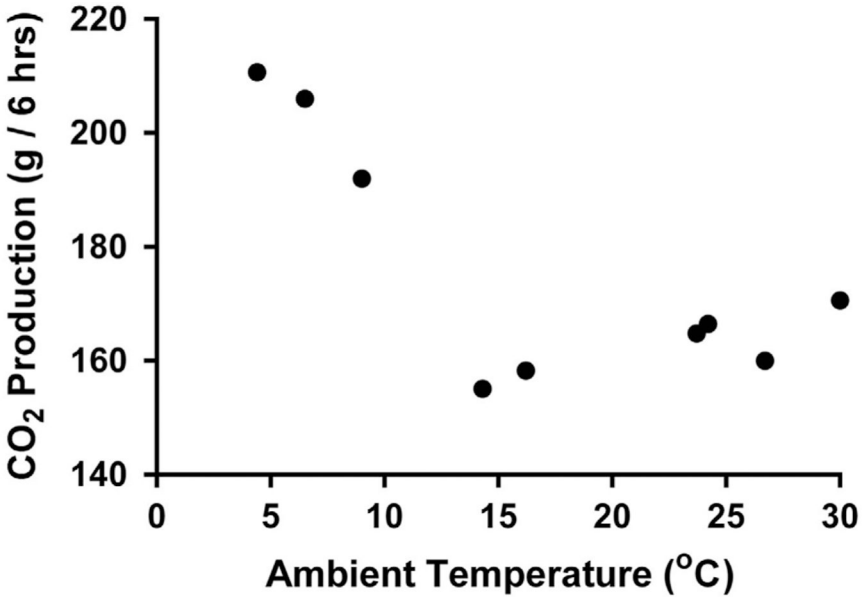

Figure 2.
Measurements of CO_2 production from one subject exposed to different ambient temperatures performed by Voit using the Pettenkofer respiration chamber in 1876.[10]

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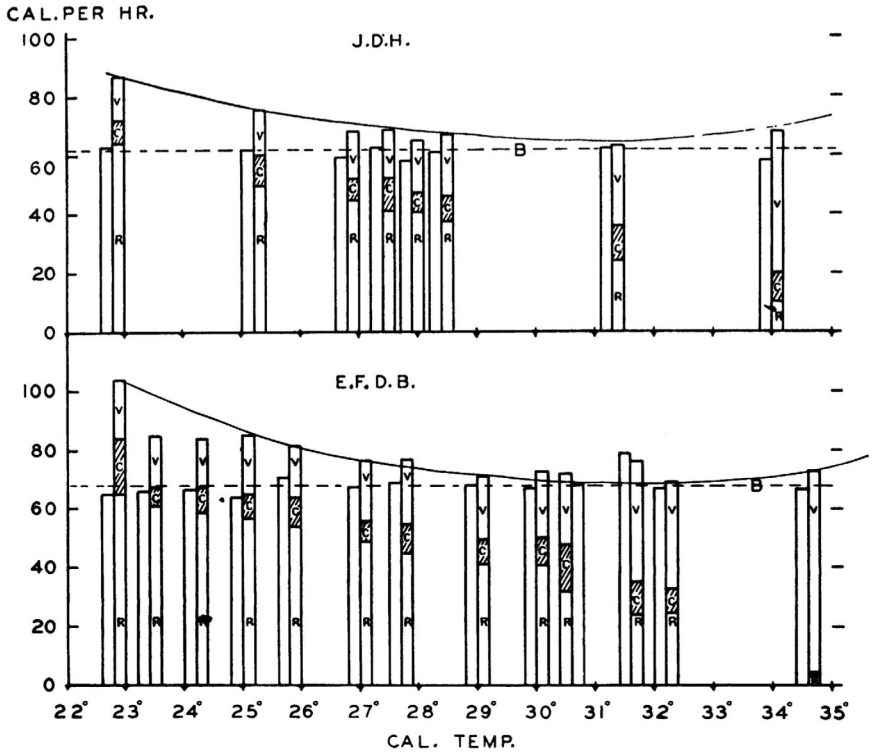

Figure 3.

Measurements of heat loss and production in two subjects exposed to different ambient temperatures performed by Hardy and Dubois[13] using the Russell Sage calorimeter in 1937. Figure taken from JD Hardy and EF Dubois, 1937.

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Table 1.

A brief summary of CIT measured by room calorimetry (metabolic) chambers[a]

CIT (avg % increase)	Subjects	Cold exposure conditions	Exposure medium	Temperature range (°C)	Insulation (Clo)	Year	Authors
36[b]	1 'strong' man	6 h sitting	Air	4.4–30[c]	NS	1878	Voit[10]
11	21 men and women	1.2 h supine	Air	2, 24	~ 1.0	1932	Swift[11,12]
0 (no consistent trends)	2 men (thin man and fat man)	2.5 h semireclined resting	Air	16.6–33.1[c]	0 (only 'atheletic supporter')	1936	Winslow *et al.*[52,53]
0	2 men	2.5 h supine	Air	22.5–35[c]	0	1937	Hardy and Dubois[13]
0	2 men	Semireclined resting	Air	6.8–35.5[c]	0	1937	Winslow *et al.*[14]
7.5 for 'responders'	13 women	2.5 h supine	Air	22–35[c]	0	1952	Dubois *et al.*[15]
7	9 women	30 h daily living	Air	22, 28	0.6	1981	Dauncey[54]
5	4 men, 6 women; young	24 h standardized activity	Air	20, 28	~ 0.23 (28 °C, daytime); more at nighttime, more in 20 °C)	1990	Warwick and Busby[28]
8.5	8 normal weight females	48 h daily living	Air	22, 27	NS	2001	van Marken Lichtenbelt *et al.*[31]
5	9 men	24 h daily living	Air	16, 22	>0.71	2002	van Marken Lichtenbelt *et al.*[55]
5.7	9 lean young men	60 h daily living	Air	16, 22	1.2 daytime 7.0 nighttime	2002	Westerterp-Plantenga *et al.*[56]
8	10 men	60 h daily living	Air	16, 22	>0.71	2002	Schrauwen *et al.*[57]
10.0	8 lean young women	48 h daily living	Air	22, 27	0.6 daytime, 7.0 nighttime	2002	Westerterp-Plantenga *et al.*[58]
5.1	13 lean men	36 h at 22 °C, 84 h at 16°C, daily living	Air	16, 22	NS ('standardized clothing')	2007	Wijers *et al.*[59]
2.8	11 lean men	34 h at 22 °C, 82 h at 16 °C, daily living	Air	16, 22	NS ('standardized clothing')	2008	Wijers *et al.*[60]
13.7 for lean, 17.2 for obese	10 lean, 14 overweight/obese young men	1 h at 22 °C, 2 h at 16 °C	Air	16, 22	0.49	2009	van Marken Lichtenbelt *et al.*[38]
1 for group, 2.2 for lean, 0 for obese	9 lean, 10 obese men	36 h at 22 °C, 48 h at 16 °C, daily living	Air	16, 22	0.8 daytime 7.0 nighttime	2010	Wijers *et al.*[30]
5.9	15 men, 10 women	12 h daytime, sitting	Air	19, 24	0.55	2010	Celi *et al.*[61]
3.5	10 lean men	24 h daily living	Air	16, 22	0.8	2011	Wijers *et al.*[62]
5.3	14 men, 10 women	12 h night sleeping	Air	19, 24	0.65	2013	Chen *et al.*[40]
6	5 men	24 h daily living	Air	19, 24	0.55	2014	Lee *et al.*[47]

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Abbreviations: CIT, cold-induced thermogenesis; NS, not stated.

[a] In healthy human subjects exposed to cold vs warm room air temperatures in a laboratory setting.

[b] Estimated from a figure.

[c] Multiple temperature points measured over the range.

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Table 2.

A brief summary of CIT measured by portable metabolic devices (metabolic carts or Douglas bag)[a]

CIT (avg % increase)	Subjects	Cold exposure conditions	Exposure medium	Temperature range (°C)	Insulation (Clo)	Year	Authors
55	4 men	3 h sitting	Air	10, 26.6	0.08	1960	Buskirk *et al.*[16]
~67% (summer), ~45% (winter) (non-acclimated)[b]	10 men (summer), 6 men (winter)	2 h supine	Air	11.8, ?	0	1961	Davis[32]
13.1 (eskimos), 0 (non-eskimos)	6 eskimos, 6 non-eskimos	3 h seated	Air	23–35[c]	~ 0.08	1962	Rennie *et al.*[63]
~ 280[b]	9 men (measurements taken from 20, only measurements from 9 are reported)	2 h supine	Air	1, ? (thermal neutrality with blanket)	0	1992	Vallerand *et al.*[64]
~ 68[b]	8 men	4 h sitting	Air	10.0–22	0.1	1998	Young *et al.*[22]
11.5 winter, 7.0 summer	10 women, 10 men, young, BMI 17–32 kg/m^2	1 h at 22 °C, 45 min of cooling, 3 h at 15 °C, semisupine	Air	15, 22	0.71	2004	van Ooijen *et al.*[65]
11.8 for group, 17.2 for lean, 6.4 for overweight	10 lean, 10 overweight young men	1 h at 15 °C+duvet, 1 h at 15 °C – duvet	Air	15 (+duvet = warm/− duvet = cold)	0.71, duvet = 0.68	2006	Claessens-van Ooijen *et al.*[29]
17	10 men	2 h supine	Air	Individualized to just above shivering, 23–25	0.49	2012	Vosselman *et al.*[66]
13	6 men	2 h supine	Air	Individualized to just above shivering, 23–25	0.49	2013	Vosselman *et al.*[67]
11.8 for untrained, 8.0 for trained	12 endurance-trained and 12 untrained	2 h supine	Air	Individualized to just above shivering, 23–25	0.19	2015	Vosselman *et al.*[68]
10.9	36 lean young men	1.5 h semisupine	Air	15.8 ± 1.9, 25.9 ± 1.6	0.36–0.42	2016	van der Lans *et al.*[69]
28 for BAT+, 2.9 for BAT −	13 young men (6 BAT+/7 BAT −)	2 h seated	Air +intermittent ice block	19+intermittent ice block, 27	0.21	2011	Yoneshiro *et al.*[70]
18 for BAT+, 5.2 for BAT −	27 young men (27 BAT+/24 BAT −)	2 h seated	Air +intermittent ice block	19+intermittent ice block, 27	'Light clothing'	2013	Yoneshiro *et al.*[49]
5.5	4 men, 6 women	2 h reclining	Air+water-perfused vest	20 (room)+14 (circulated water), 23 (room)	0.44	2012	Cypess *et al.*[71]
8	12 men (BAT+)	2 h reclining	Air+water-perfused vest	20 (room)+14 (circulated water), 23 (room)	0.44	2015	Cypess *et al.*[72]

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CIT (avg % increase)	Subjects	Cold exposure conditions	Exposure medium	Temperature range (°C)	Insulation (Clo)	Year	Authors
91 for lean, 26 for overweight[b]	6 normal weight, 2 overweight/obese young men	≤ 2.5 h seated, submerged to neck	Water immersion	8–38[c] (individualized low temperature)	~ 0.04 (immersed) +fleece-lined helmet	1960	Cannon and Keatinge[21]
5.7 (eskimos), − 2.6 (non-eskimos)	5 eskimos, 5 non-eskimos	1 h immersed except for faces	Water immersion	33, 35	NS	1962	Rennie *et al.*[63]
Up to 70[d]	10 men	< 1 h, water immersion	Water immersion	24–38[c]	0.08	1966	Craig and Dvorak[19]
16–50	10 men	2 h	Water-perfused blankets	12–27[c]	0.55	2014	Lee *et al.*[73]
77	6 men	2.5 h supine	Water-perfused suit	18, 25	NS	2012	Ouellet *et al.*[41]
11.0 for women, 11.6 for men	9 women, 8 men, lean young	50 min cooling+30 min non-shivering cold	Water-perfused suit	25.4 ± 1.8 (personalized), ? ('thermoneutral')	NS	2013	van der Lans *et al.*[48]
67–83	25 men	3 h	Water-perfused suit	−4 (skin temp), 24 (warm)	0.08	2015	Blondin *et al.*[42]

Abbreviations: BAT, brown adipose tissue; BMI, body mass index; CIT, cold-induced thermogenesis; NS, not stated.

[a] In healthy human subjects exposed to cold vs warm temperatures in a laboratory setting.

[b] Estimated from a figure.

[c] Multiple temperature points measured over the range.

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