

Metabolic requirements of shivering humans

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1. ABSTRACT

This review examines the heat production component of thermoregulation in adult humans. It describes the energy requirements of shivering muscles as they attempt to provide sufficient heat to counterbalance increases in heat loss in cold environments. Emphasis is placed on types of metabolic substrates used under various shivering conditions as well as on the effects energy deficit and food consumption. During shivering, muscle recruitment intensity and pattern of fiber recruitment are highly variable between muscles and individuals. In addition, a number of studies have indicated that shivering can be sustained with different fuels for several hours under variable conditions of cold stress and CHO availability. However, little is still known on the effects of prolonged fasting and energy deficit in the cold on energy metabolism. Even though it is clear that food consumption increases the odds for survival, the metabolic fate of ingested substrates remains highly uncertain. Combining fundamental principles surrounding metabolic fuel selection with applied knowledge of human performance in the cold may allow important breakthroughs in this field of research.

2. INTRODUCTION

Since their origin on Earth, living organisms have faced the biochemical challenges associated with fluctuations in environmental temperatures. Changes of a few degrees are sufficient to disrupt appropriate structure of macromolecules, reduce enzyme efficiency and modify adequate metabolic fluxes. Within the animal kingdom, two main temperature adaptations have emerged to provide short- and long-term solutions to defend cells against loss of function (1). Ectotherms, the vast majority of species, have been extremely successful at maintaining their core temperature in close relation to ambient temperature and using behavioral strategies to select, whenever possible, an optimal survival temperature. In contrast, the other group, endotherms (*i.e.* birds and mammals) have evolved to regulate body temperature within a narrow range at a specific set point ranging from 36 to 38°C (2). In those animals, core temperature fluctuations exceeding lower or upper critical limits can have disastrous consequences. Depending on the duration and the severity of the heat stress, it may result in temporary loss of function, permanent cell damage or even death. Maintaining a constant body temperature provides stability for neural

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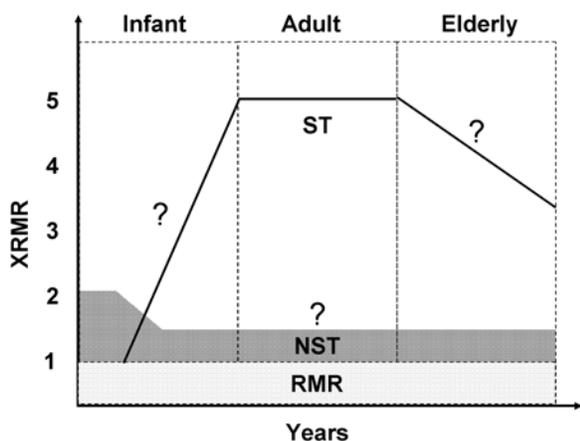


Figure 1. Schematization of the respective contributions of nonshivering thermogenesis (NST) and shivering thermogenesis (ST) throughout life (age in years). Question marks (?) indicate areas where information is lacking or uncertain. Metabolic rates are expressed relatively to resting metabolic rate (RMR) and are presented on the Y-axis.

function and prevents large fluctuations in the rates of vital processes even in the face of large modifications in ambient temperature (1). While the advantages of endothermy are clear, conserving a high temperature comes at a considerable energy cost. In fact, metabolic rate of endotherms may be more than one order of magnitude higher than that of their ectothermic counterparts (2). For example, Else and Hulbert (3) compared an ectotherm and an endotherm of similar body weight and body temperature. The ectothermic reptile (*amphibolurus nuchalis*) displayed metabolic rate 8-fold lower than the endothermic mouse (*mus musculus*). This higher metabolic cost in endotherms is associated with a greater need to obtain and assimilate substantially higher amounts of food in order to survive.

Among endotherms, humans have acquired efficient physiological defenses to dissipate heat in warm climates. However, their furless body does little to prevent extensive heat loss in cold environments. These thermoregulatory adaptations would have made the expansion of early hominids from African grasslands to colder climates impossible without adequate strategies to assist in the reduction of heat loss (e.g. building shelters, wearing clothing, mastering fire)(4). When exposure to cold temperatures is inevitable, humans must rely on the concerted activation of physiological processes that increase heat production and lower heat loss. This review examines the heat production component of thermoregulation in adult humans. More specifically, it describes the energy requirements of shivering muscles as they attempt to provide sufficient heat to counterbalance increases in heat dissipation in cold environments. Particular emphasis is placed on the types of metabolic substrates used under various shivering conditions as well as on the effects energy deficit and food consumption on the metabolic requirements of shivering.

3. HEAT PRODUCTION IN COLD EXPOSED HUMANS

Thermogenesis occurs in all tissues of the body and is an inherent by-product of metabolic activity through the inefficiency of biochemical reactions. Under basal conditions, humans produce on average ~5 kJ of heat per kilogram per hour; a thermogenic rate sufficient to counterbalance the rate of heat loss under basal conditions and maintain an average core temperature of ~37°C. During cold exposure, maintaining core temperature requires an increase of the thermogenic rate aimed at counteracting rises in heat loss. This increase in thermogenesis is achieved voluntarily through exercise or involuntarily by the activation of non-shivering thermogenesis (NST) and/or shivering thermogenesis (ST). Exercise provides by far the highest potential increase in thermogenic rate reaching values 15 to 20 times above basal metabolic rate or BMR; thermogenic rate during exercise can reach values of ~100 kJ·kg⁻¹·min⁻¹. However, in cold environments, exercise is not always possible or advisable due to overexertion or to low food supplies. Under such situations, activation of NST and/or ST is essential for maintaining core temperature. The respective contribution of NST and ST to total heat production during cold exposure varies greatly throughout life but much work remains to quantify the exact role of these two mechanisms across ages (Figure 1). NST may take various forms including the activation of thermogenic tissues (e.g. energy uncoupling in brown adipose tissue or BAT)(5), the stimulation of futile cycles (e.g. TAG/NEFA cycle)(6), the activation of spontaneous physical activity (like fidgeting and postural changes) which are components of non-exercise activity thermogenesis or NEAT (7) and/or the heat dissipation through food assimilation (i.e. thermic effect of feeding or TEF)(8). In newborn humans where muscle mass is small and surface-to-volume ratio is high, the role played by NST is of particular importance and is associated to the activation of large superficial and deep BAT depots (9). In the cold, the activation of these BAT reserves is sufficient to double basal heat production (5). While it is clear that NST is an essential mean of heat production in newborn humans, the exact contribution of this pathway in adults remains controversial. It has generally been assumed that the presence of BAT decreases rapidly after the first year of life thus reducing significantly the contribution of NST. However, recent evidence in adults suggests that role of NST through the activation of BAT might be higher than previously thought. Research has shown that a minority of individuals still retain significant amounts of BAT (10-13). Using integrated positron-emission tomography and computed tomography (PET-CT), BAT volume was estimated at ~130 cm³ in lean men and ~80 cm³ in overweight or obese men (11). Both quantity and metabolic activity of BAT are highly variable among individuals and are inversely related to body mass index and percent body fat (11). Even though the presence of BAT deposits in adults has now been clearly established, much work remains to quantify the exact thermogenic capacity of this tissue during cold exposure. In rats, it is estimated that 50 g of active BAT are sufficient to produce 1.8 kJ of heat per min or 2562 kJ per day (Dulloo, A.

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personal communication); this assumes that this tissue consumes 1.7 ml of oxygen per g per min (14) and that each litre of oxygen consumed correspond to ~20.93 kJ of heat produced. If similar BAT activity was possible in humans, maximal activation of this tissue could provide up to 25% of all the heat produced during low to moderate intensity shivering; assuming an oxygen consumption rate of 800 to 1000 ml·min⁻¹ in the cold (15), that a lean individual possesses 130 cm³ of BAT at a density of 0.9 g·cm³. However, it is likely that the activity of BAT in humans is much lower than in rats; rats have much higher surface-to-volume ratios. Nonetheless, the role of NST in human body temperature regulation in response to cold cannot be ignored as suggested by cold acclimation (16) and hypoxic hypoxia experiments (17). Even though aspects of NST are fascinating, this review will focus mainly on the ST component of heat production in adult humans.

4. WHAT IS SHIVERING THERMOGENESIS?

Of all tissues, skeletal muscles show the greatest plasticity. They can operate over a large range of internal conditions (e.g. temperature, pH, oxygen availability) and can be chronically modified in response to changes in external pressures such as increased work rate or inactivity. Across animal species, from the smallest insect to the largest mammal, the main function of skeletal muscles is to drive locomotion in order to acquire food and to escape predation (18). Through evolutionary times, this tissue has also played a key role in ensuring survival in cold environments by stimulating heat production via voluntary contractions and/or ST. Under the control of the sympathetic nervous system, ST generates heat through involuntary, rhythmic muscle contractions (19). ST stimulation is regulated by feedforward mechanisms activated by peripheral thermoreceptors (20-22). During cold exposure, peripheral thermal afferents reach the pre-optic area of the hypothalamus via the lateral parabrachial nucleus likely resulting in a disinhibition of neurons in the dorsomedial hypothalamus which stimulates neurons in the rostral medullary raphe (17, 19-22). In response, the rostral medullary raphe neurons activate the fusimotor fibres (20, 23, 24) which ultimately results in the onset of shivering (20, 24-27). The intensity of shivering has been associated with cold exposure duration and severity as well as with the adiposity and surface-to-volume ratio of individuals (28-30). It has been reported that maximal ST in adult humans can reach intensities equivalent to ~40% of maximal oxygen consumption or ~25 kJ·kg⁻¹·min⁻¹ or ~5 times resting metabolic rate (X RMR) (30). Still to date, however, the metabolic and/or neuromuscular reasons for this upper limit in maximal ST are unknown. Interestingly, the thermogenic scope of humans, or maximal shivering metabolic rate divided by basal metabolic rate (BMR), is similar to values found in birds; another animal which can display a significant contribution of NST early in life (31-33) but relies to a large extent on ST later in life. In 37 avian species, maximal thermogenic rate in the cold reaches on average almost 6-times BMR (ranging from ~4.5 to ~8.3 X BMR) and is consistent along a wide range of body masses (~6 g to 980 g)(34). Assuming that the

aerobic scope in birds, or the maximal oxygen consumption in flight divided by BMR, is ~15 X BMR (see 35 for review), this would represent an average maximal ST intensity similar to the one found in humans (~40%VO₂max). The question remains, why does ST consistently plateau at values three times lower than maximal aerobic capacity? Cold exposure generally results in minimal changes in heart rate and blood pressure. These hemodynamic responses may prevent the capacity to reach higher oxygen consumptions at the tissue level and thus, higher thermogenic rates. In addition, research has also shown that high ST intensities interfered with voluntary movements (36, 37). Perhaps, through evolutionary times, lower shivering intensities produced sufficient heat to increase odds of survival without compromising locomotion and ultimately survival.

Using electromyography (EMG), researchers have been able to quantify shivering intensity as well as electrophysiological characteristics of each shivering muscle. Within individual muscle, the EMG signal can be separated into two components based on differences in intensity [2-5 vs. 7-15 % of maximal voluntary contraction (%MVC)] and rate of occurrence (8-10 vs. 0.1-0.2 Hz)(38, 39). Continuous, low-intensity shivering is related to low-threshold fibers (type I, specialized for lipid use) while high-intensity bursts are associated with high-threshold fibers (type II, specialized for CHO use)(37). Even though the physiological significance of this dual pattern remains unclear, it has been shown to play a key role in orchestrating fuel selection (39). EMG analysis also revealed that muscle shivering activity varies greatly amongst individuals and muscles (39, 40). Even when subjects are normalized as much as possible for morphology, percent body fat, diet and level of cold-acclimation (39), large inter-individual differences in the relative contributions of muscles to total shivering intensity and shivering EMG pattern are observed. Figure 2 exemplifies such muscle recruitment variations in burst shivering rate and intensity in two morphologically similar men shivering at moderate intensity (3.5 X RMR). Even though differences are seen between muscles, shivering activity occurs in a symmetrical manner displaying similar burst activity (preliminary results in women; Figure 3). Comparisons were also made between men and women (Figure 4). While burst shivering rates are similar in all muscles, women display higher shivering intensity than men at the same given metabolic rate in the cold (2.5 X RMR; Figure 4). This difference in intensity is most likely related to the need to a greater number of more motor units to produce the same thermogenic rate when compared to men. Much work remains to better understand the physiological reasons and the significance of these inter- and intra-individual variations in muscle recruitment. For example, what is the neuromuscular basis for the dual shivering pattern, burst vs. continuous shivering? In birds, it has been suggested that it may be an inherent consequence of the mixed fiber composition of skeletal muscles (41). More anaerobic muscles, high in type II fibers, tend to shiver in bursts whereas those relying more on aerobic metabolism, high in type I fibers, shiver more continuously (42). In humans, fiber composition varies

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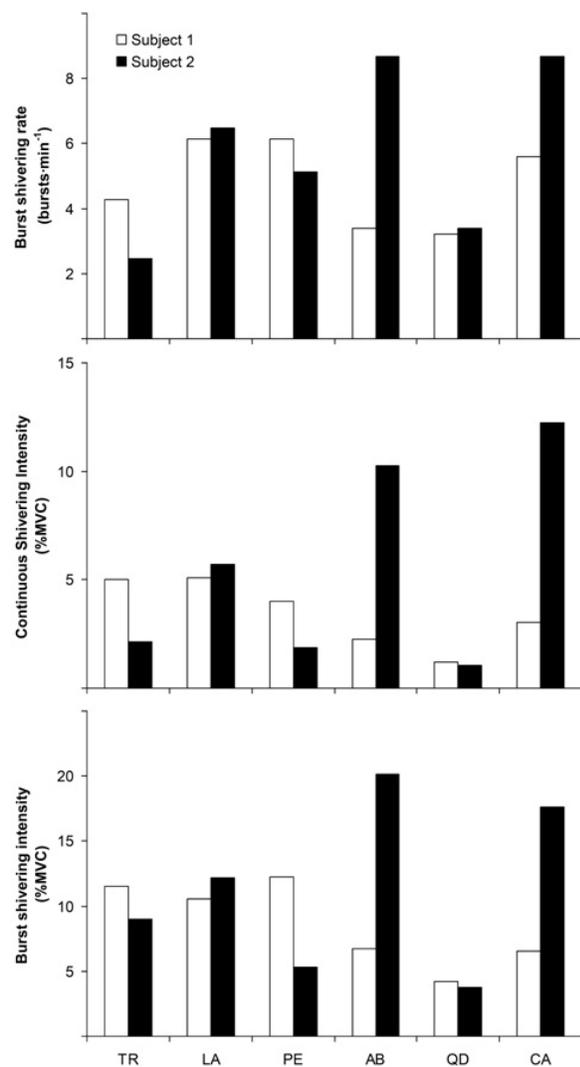


Figure 2. A. Burst shivering rate (number per min), B. burst shivering intensity (%MVC) and C. continuous shivering intensity (%MVC) measured in the last 15 min in two non-cold acclimatized men shivering at moderate intensity (3.5X RMR). Measurements were made in 6 muscles: *trapezius* (TR), *latissimus dorsi* (LA), *pectoralis major* (PE), *rectus abdominis* (AB), quadriceps (QD) and *gastrocnemius* (CA). Subjects had similar age, body surface area, fat percentage and aerobic capacity.

significantly among muscles and individuals (43, 44). Whether these difference in fiber composition dictate variations in EMG shivering pattern in human remains to be established.

5. FUELING SHIVERING THERMOGENESIS

The ATP required for maintaining ST is obtained through the combined oxidation of carbohydrates (CHO), lipids and proteins. The contribution of each fuel to the total thermogenic rate is influenced by differences in shivering intensity (15, 45), variations in muscle fiber recruitment or burst shivering rate (39) and changes in the

size of CHO reserves prior to cold exposure (46-48). Each metabolic fuel source presents distinct differences in their biochemical properties and in the size of their reserves (see 49 for review). For example, when compared to lipids, maximal ATP production rate from CHO is achieved faster (<2 min for CHO vs. >30 min for lipids) and reaches higher values (30 $\mu\text{mol ATP g}^{-1} \text{min}^{-1}$ for CHO vs. 20 $\mu\text{mol ATP g}^{-1} \text{min}^{-1}$ for lipids). In contrast, lipids are by far the most abundant representing over 85% of total energy reserves (vs ~1% for CHO and ~14% for proteins) and have an energy potential more than twice as high as CHO and proteins (~41 kJ/g for lipids vs ~16 kJ/g for CHO and ~20 kJ/g for proteins). However, the availability of these fuels will depend on the degree of adiposity as well as on their nutritional status of the individual. It is generally assumed that oxidizing the appropriate combination of these fuels is essential to sustain energy production under specific environmental conditions. Substantial changes in the size of energy reserves may result in reduced capacity to maintain appropriate ATP production (see Energy balance and shivering response). Mechanisms of fuel selection during low and moderate ST have been described in detail previously (see 50, 51 for review). The following section provides an overview of the role played by individual metabolic fuels in sustaining shivering muscles. It will also identify gaps in this field of research, provide new information and suggest future directions of investigation.

In cold exposed adult humans, most fuel selection measurements to date have been performed in 12-h post-absorptive, non-cold acclimatized men during low intensity (2 to 2.5X RMR) and moderate intensity shivering (2.5 to 3.5X RMR)(see 51 for review) as well as during hypothermic recovery (45); few measurements are available in women in these conditions (see 5.1. Metabolic requirements of shivering women). Figure 5 presents absolute rates and relative contribution of CHO and lipids to total heat production measured during low and moderate intensity shivering (15) and during hypothermic recovery (45). During low-intensity shivering in non-cold acclimated men with normal glycogen reserves, results showed that lipid oxidation rate was stimulated by as much as 4-fold and accounted alone for half of heat produced (50 % H_{prod} vs. 40 % H_{prod} for CHO and 10% H_{prod} proteins)(52). As shivering intensified from low to moderate-intensity, CHO oxidation was responsible for the entire increase in thermogenic rate, because rates of lipid and protein oxidation remained constant (15). Similarly, during hypothermic recovery, ST was supported to a larger extent by CHO at all intensities above 50% of maximal shivering intensity (or 3 X RMR) while lipid utilization became dominant below this level (45). Together, these studies showed that the regulation in fuel selection during ST is modulated entirely by changes in CHO oxidation rate which can increase by as much as 10-fold from baseline to maximal shivering. In contrast, lipid oxidation rate always remained constant reaching a maximum rate of ~200 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at low shivering intensity (~20 % $\text{VO}_{2\text{max}}$ or ~2.5X RMR); a value more than 3 times lower than reported for sustained exercise (53). The findings from these studies have also shown that protein oxidation rate is not affected by cold exposure. However, this fuel source may still account for ~7 to 25% of all the heat generated depending on the nutritional status of subjects (15, 46).

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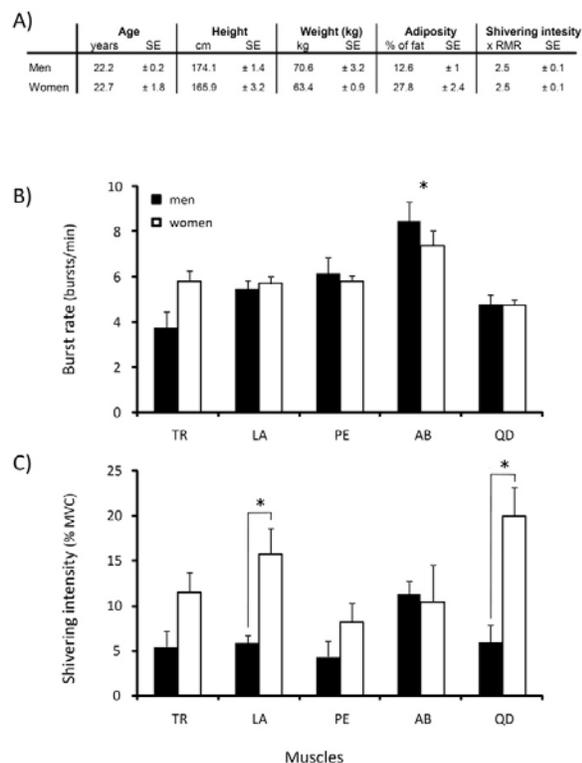


Figure 3. Bilateral symmetry in shivering thermogenesis measured in 5 muscle pairs: trapezius (TR), latissimus dorsi (LA), pectoralis major (PE), rectus abdominis (AB), and quadriceps (QD) of non-cold acclimatized women. Sides are presented in the anatomical position; right side (filled bars) and left side (open bars).

It is important to note that the pattern of fuel selection described for cold exposure is distinctly different from the one generally observed during exercise (54). A detailed comparison of absolute rates and relative contributions of CHO, lipid, muscle glycogen and plasma glucose measured during shivering (15) and during exercise (55) has been presented previously. Briefly, oxidation rates of all the fuels are 2 to 7 times lower for shivering than for exercise consistently with the large difference in metabolic rate (1 to 5 X RMR for shivering vs. 1 to 20 X RMR for exercise). In addition, the much higher reliance on CHO observed during ST is not compatible with the well known fuel selection pattern of exercise especially when considering the relatively low metabolic rates elicited by shivering (~30%VO₂max). Together, the observations indicate that shivering and exercise of similar energy requirements appear to be supported by different fuel mixtures. This divergence has been attributed to important differences in muscle fiber recruitment whereby proportionally more type II, glycolic fibers are recruited at much lower metabolic rates in the cold (15).

5.1. Metabolic requirements of shivering women

While metabolic requirements of ST in men have been studied extensively, most cold exposure research in women has focused on the effects of the menstrual cycle on thermoregulatory responses (56-60). This work

demonstrated that shivering responses of women is attenuated in the luteal phase (LP) compared to the follicular phase (FP). This difference was attributed to a higher baseline mean core body temperature in LP than FP (56, 58, 61). In contrast, little information is available on the metabolic requirements of shivering women. Out of the seventeen studies that quantified fuel selection during ST (see 51 for review), only three have estimated substrate utilization in women (57, 62, 63) and only one examined the effects of the menstrual cycle on fuel selection in the cold (62). During low-intensity shivering, Glickman-Weiss *et al.* (62) showed that hormonal fluctuations associated with the menstrual cycle had no effect on fuel selection between the luteal phase (LP) and follicular phase (FP)(62). These studies also compared fuel utilization in shivering women and men. Subjects were normalized as much as possible for body composition and aerobic capacity; comparisons were made with women in FP. Even with these precautions, findings remained unclear. While Petit *et al.* (1999) showed a greater reliance on lipids in women (~36 %H_{prod} for CHO and ~64 %H_{prod} for lipids) than in men (~47 %H_{prod} for CHO and ~53 %H_{prod} for lipids) during low intensity shivering, no sex difference in fuel selection was found in the two other studies during low- and moderate-intensity shivering (62, 63).

In contrast to cold exposure, far more attention has been given to the effects of the menstrual cycle and sex differences on substrate utilization during exercise. While many studies demonstrated a preference for lipids in LP compared to the FP (64-66), others reported no differences (67-69). Generally, however, menstrual cycle effects are seen at low-intensity exercise but not at higher work rates (64, 67, 70-73). Researchers caution that substrate utilization measurements are greatly confounded in the literature due the different methods of menstrual cycle phase identification. Even though results on the effects of the menstrual cycle phase on energy metabolism are somewhat conflicting, exercise studies have consistently demonstrated that women oxidize more lipids than men (74-79). This increased rate of lipid oxidation was attributed to the higher estrogen level found in women. Interestingly, Hamadeh *et al.* (2005) showed that males treated with 17-β-estradiol responded similarly to women in the preferential use of carbohydrates over lipids during exercise. In view of these results during exercise, additional work is clearly needed to better understand the effects of the menstrual cycle and sex differences on the energy requirements of shivering.

6. ENERGY BALANCE AND SHIVERING RESPONSE

Modifications in energy expenditure and dietary intake can considerably influence the quality and quantity of available energy substrates. Of all metabolic fuels, CHO reserves are the most vulnerable to acute changes in energy expenditure and dietary manipulations because they represent only ~1% of total fuel reserves but still play an important role in maintaining ATP production. For instance, the depletion of muscle glycogen reserves is well known to limit endurance and performance during

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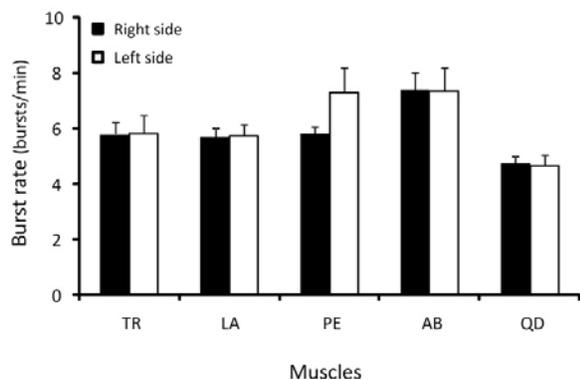


Figure 4. Shivering thermogenesis variability in B. burst shivering rate and C. shivering intensity of 5 muscles: trapezius (TR), latissimus dorsi (LA), pectoralis major (PE), rectus abdominis (AB), and quadriceps (QD) measured in non-cold acclimatized men (filled bars) and women (open bars) exposed during low-intensity shivering. Morphological characteristics and shivering intensity during cold exposure are presented in A. * significant differences $p < 0.002$.

prolonged exercise (54). During shivering, researchers have assumed through empirical evidence that the end of shivering would also coincide with the depletion of muscle glycogen reserves (80, 81). To better understand the importance of CHO reserves on shivering response, a series of studies were conducted to quantify the respective contribution of muscle glycogen and plasma glucose to total heat production: 1) during prolonged low- and moderate-intensity shivering (15, 52), 2) following the depletion and loading of glycogen reserves (46) and 3) in individuals displaying a wide range of muscle recruitment patterns (39). Results indicated that available muscle glycogen always provides most of the glucose required to sustain CHO oxidation (~75-80% of total CHO oxidation) whereas the contribution of plasma glucose remains constant at ~20-25%. While these measurements clearly showed that muscle glycogen plays an essential role for sustaining energy demands in the cold, no studies to date have been able to demonstrate that acute depletion of CHO reserves through exercise and dietary manipulations reduces shivering capacity (46, 47, 82). Using combined metabolic and electrophysiological approaches, Haman *et al.* (46, 82) showed that humans are able to sustain a constant thermogenic rate by oxidizing widely different types of fuels without modifying shivering pattern (i.e. intensity, burst vs. continuous shivering). When the contribution from CHO is reduced, utilization of lipids and proteins is stimulated sufficiently to maintain heat production. However, could shivering capacity be maintained following extended periods of energy deficits such as underfeeding, fasting and/or exertional fatigue?

Most studies aimed at identifying the effects of energy deficits in the cold have focused on changes in thermoregulatory responses and not on energy requirements of ST. An early study by MacDonald *et al.* (83) quantified changes in thermoregulatory responses of 12- and 48-hour fasted subjects exposed to five progressively reduced levels

of cold stress. They showed that core temperature was lowest in a prolonged unfed state (48-h fast), despite eliciting a greater metabolic rate at rest in ambient conditions and throughout the graded cooling. This lowered core temperature was largely attributed to an elevated rate of heat loss as indicated by greater forearm blood flow compared to the 12h fasted group suggesting that there was a blunted vasoconstrictive response in the 48-h fasted group. The elevated metabolic rate displayed at rest is typically observed in individuals fasted for 36-48 h exposed to ambient conditions (84-86) and is thought to be a transient response attributed to substrate cycling (i.e. triglyceride-fatty acid and alanine-glucose cycling and the Cori cycle) common in the gluconeogenic phase of prolonged fasting (87), returning to pre-fasted levels after more prolonged starvation [72-h; (84)]. However, it is unclear whether the elevated metabolic rate observed in the 48-h fasted group was simply due to fasting alone or an effective response to the increased heat loss. Later, Young *et al.* (88) and Castellani *et al.* (89) showed that chronic energy deficits from underfeeding and strenuous military training lasting longer than 48-h (84-h to 61 days) can limit the ability to maintain a thermal balance by blunting metabolic heat production and the insulative capacity due to the loss of both lean and fat mass. However, these detrimental effects on thermogenic rate were shown to be restored following a 48-h period of rest and refeeding (88). Nevertheless, these subjects continued to display an inability to reach thermal balance potentially due to a reduced insulative capacity associated with the loss in lean and fat mass. After 108 days of recovery whereby fat and fat-free mass were re-established to similar pre-camp levels, these military recruits clearly showed an improvement in thermal responses as they were able to fully compensate during the same cold stress as displayed by a maintained rectal temperature. The improved cold tolerance and increased metabolic heat production of the 48-h re-fed and rested rangers observed by Young *et al.* (88) suggests that the diminished heat production may be due to the limited substrate availability, while a fall in glycemia typically observed in prolonged fasted individuals [from 5.2 mmol/L in 12-h fast to 3.8 mmol/L in 60h fast; (90)] exposed to ambient conditions might effect a diminished shivering response when exposed to a cold condition for a prolonged period (>180 min). These findings supports the premise that the ability to survive during prolonged cold exposure is dependent upon substrate availability (namely CHO availability) to maintain the drive to shiver (91) and diminish the risk of hypoglycemia which has been shown to reduce or inhibit shivering (92, 93). However, Castellani *et al.* (89) did not observe a fall in glycemia in underfed participants exposed to a cold stress for 180 min. Whether normoglycemia can be maintained for a prolonged period is still unknown but these conclusions suggest that providing supplemental exogenous substrates through feeding may be of critical importance to maintain adequate shivering thermogenesis.

6.1. Effects of food consumption

The metabolic requirements and associated dietary needs to sustain shivering thermogenesis during cold exposure have been debated extensively for decades.

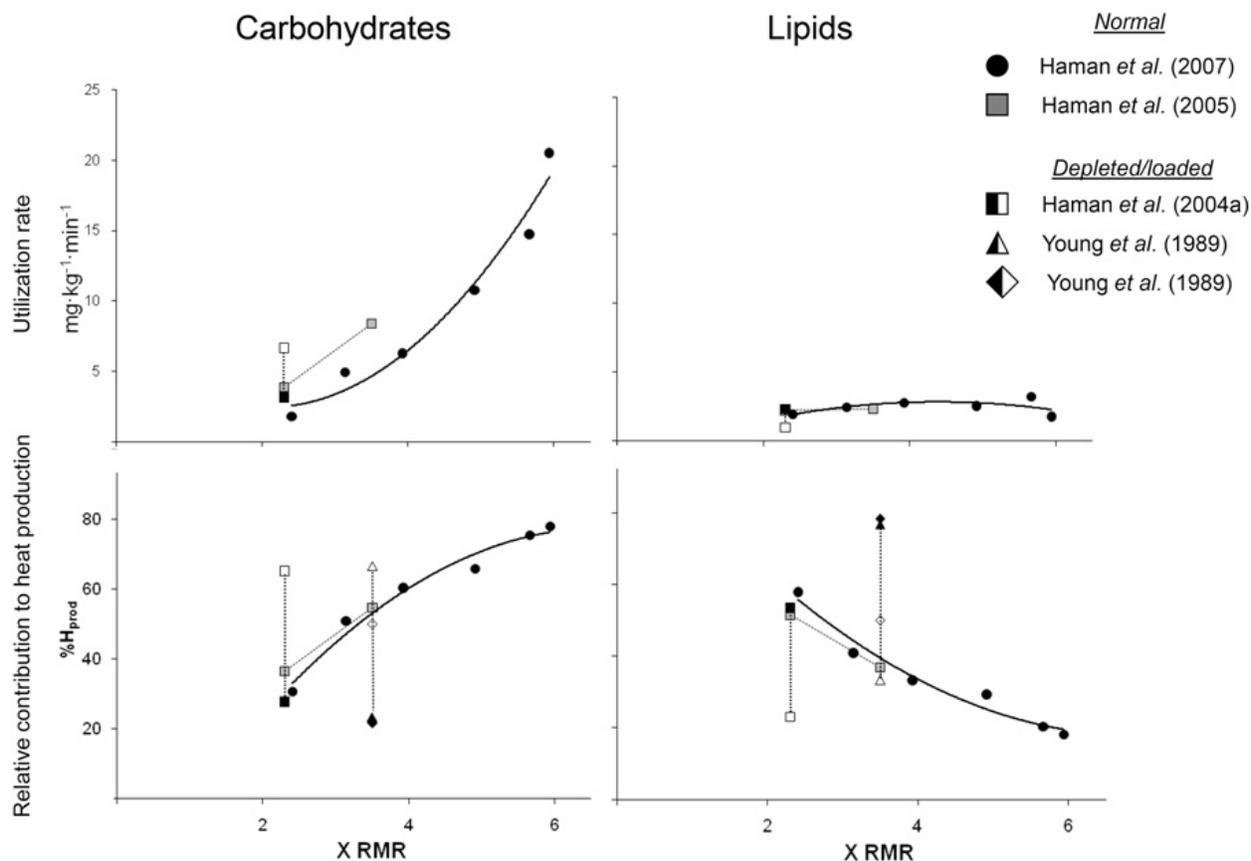


Figure 5. Absolute rates (top panels) and relative contributions (lower panels) of carbohydrates (left panels) and lipids (right panels) to total heat production reported in the literature in men with normal during low and moderate intensity shivering (gray squares) as well as during hypothermic recovery (filled circles). Values are also presented in subjects with low (black squares) and high CHO reserves (open squares) during low-intensity. During moderate-intensity shivering, only the relative contributions of CHO and lipids to total heat production are presented; not corrected to account for the contribution of proteins. Measurements were made in men with low (black triangle and black diamond) and high CHO reserves (white triangle and white diamond) during 18°C water immersion.

Prior to modernization of communities, traditional diets of indigenous northern circumpolar residents showed a greater reliance on proteins (~45%) and fats (~45%) while ingestion of CHO was low (~10%) (94, 95). Military personnel stationed in arctic and subarctic areas have traditionally voluntarily consumed a habitual North American diet containing 16% protein, 37% fat and 48% CHO (96-98), possibly due to military recommendations, food availability or simply preferential selection. Despite the known dietary habits of past Northern indigenous populations, researchers have never reached a consensus on the ideal macronutrient content required to increase the odds of survival in a cold environment (99, 100). Yet, anecdotal and empirical evidence unequivocally demonstrate that regardless of the macronutrient content of the meals, chronic underfeeding increases the susceptibility of becoming hypothermic during prolonged cold exposure by diminishing insulative and thermogenic tissue (88, 101). In addition to preserving the insulative and thermogenic capacity, ingesting food can provide supplementary substrates to complement endogenous reserves, which can modulate whole body fuel

selection during shivering (102). Additional work is needed to determine the optimal macronutrient composition of ingested foods to improve odds of survival during prolonged shivering.

It has long been speculated that the main limiting factor for survival in the cold is the depletion of muscle glycogen, leading to a reduced cold sensitivity [lowered drive to shiver (91)], or hypoglycaemia (<2.8 mM) leading to reduced or inhibited shivering thermogenesis (92, 93, 103). To date, no studies have successfully elicited such responses through prolonged cold exposure. However, there is little doubt that preserving the scarce endogenous glycogen reserves is of critical importance. Although it is well documented that when muscle glycogen reserves are reduced, lipid and protein oxidation compensate to maintain a constant rate of heat production (46), it is unclear whether this mechanism is sufficient to maintain heat production for a prolonged period, particularly if muscle glycogen, this limited resource, is still strongly mobilized. This has lead researchers to suggest that sparing CHO reserves through CHO supplementation may be an

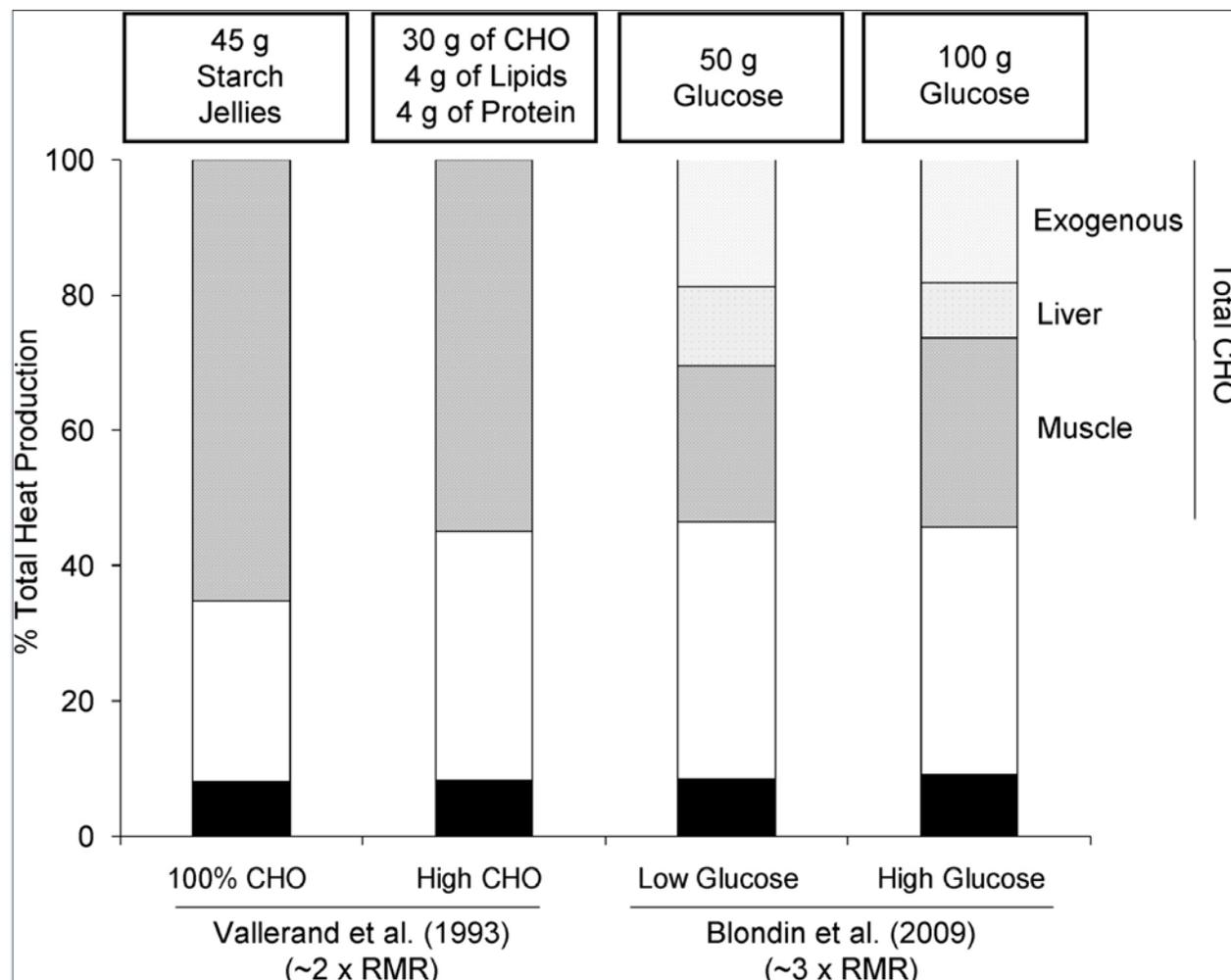


Figure 6. Relative contributions of carbohydrates (liver, muscle glycogen and exogenous), lipids and proteins to total heat production during the final 30 min of cold exposure when ingesting glucose at a low (Low Glucose) and high (High Glucose) rate (107) compared to ingesting 100% CHO or High CHO (109). Protein oxidation was assumed to be 0.07 g/min in calculated relative contribution of CHO and lipids from Vallerand *et al.* (109).

important strategy in prolonging survival time in the cold (52, 91). Few studies have investigated the effects of food consumption before or during cold exposure on thermoregulatory responses and the overall energy balance (102, 104-108). While the purpose of these respective studies varied tremendously, most of the earlier studies were directed at identifying whether ingesting CHO could increase total heat production, via the thermic effect of feeding, during shivering thermogenesis (104, 106, 108). Their findings unequivocally showed that ingesting CHO did not affect the thermoregulatory responses to cold exposure. Of these only Vallerand *et al.* (104, 109) and Blondin *et al.* (102) reported estimates of changes in CHO, lipid and protein oxidation in men during low to moderate intensity shivering (2.0 – 3.0 X RMR) following the ingestion of CHO. Vallerand *et al.* (104) showed that when cold-exposed men ingested starch jellies (712 kJ or ~45g CHO) or a high-CHO bar (712 kJ; ~30g CHO, ~4g fat and ~4 g protein), at the beginning and after 90 min of cold exposure, discernible changes in CHO and lipid utilization

were only observed when ingesting the jellies (Figure 6). A more recent study, using a combination of stable isotopes and indirect calorimetry methodologies, showed that the relative contribution of CHO to total heat production increased by ~14% and that of lipids tended to decrease to a similar extent when glucose was ingested at a rate of 400 or 800 mg/min over 2h [(102); Figure 6]. This study was also the first to partition the utilization of CHO. The utilization of liver-derived glucose decreased in a dose-dependent manner, thus sparing valuable endogenous CHO reserves, while muscle glycogen utilization did not differ from the control condition. Interestingly, the rate of exogenous glucose oxidation reached a peak and plateau of 195 mg/min at the lower ingestion rate; an oxidation rate that was one-third less than what has been reported during exercise eliciting a similar metabolic rate (110). This study also showed that 55-77% of the ingested glucose was not oxidized and thus was unaccounted for. Presumably the remaining portion was either not absorbed and/or directed towards non-oxidative disposal. Exercise studies can

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provide us with further insight into means of increasing the rate of exogenous glucose oxidation as well as increase the quantity of ingested CHO being directed to non-oxidative disposal. For instance, manipulating the timing of CHO ingestion, to illicit an insulinemic peak that coincides with the shivering steady-state, could increase glucose entry into the shivering muscles thus increasing exogenous glucose oxidation and non-oxidative disposal. Further, ingesting multiple transportable CHO (glucose with fructose) could increase this rate of exogenous glucose oxidation even further (see 111 for review) while also potentially significantly increasing non-oxidative disposal thanks to the gluconeogenic properties of fructose metabolism.

The thermoregulatory differences between exercise and cold exposure could be the most significant contributing factors to the differences in exogenous substrate utilization observed between these two conditions. In addition to differences in muscle recruitment patterns mentioned earlier in this review, cold exposure stimulates vasoactive responses which serve to create an insulative shell to reduce the thermal conductance between the environment and the core (112). Veicteinas *et al.* (113) previously showed that 10-15% of the overall body tissue insulation stems from the diminished perfusion of skin and subcutaneous fat when immersed in water, at a temperature eliciting no increase in metabolic rate (termed critical water temperature). The remaining proportion has been attributed to a reduced blood flow in muscles. As blood flow increases with the increase in heat production (from onset of exercise or shivering), total body insulation progressively falls as a function of the metabolic rate elicited (114, 115). However, this increase in blood perfusion is likely significantly lower than what is found during exercise of the same metabolic rate performed in ambient conditions. Could glucose entry into the muscle be the main mechanism limiting exogenous glucose oxidation? This question remains unanswered. Could intestinal absorption be limiting exogenous glucose oxidation? Animal models suggest that blood flow to the small intestine during cold exposure, inducing a metabolic rate two-times that of resting metabolism, is reduced by 30-50% of that seen in a thermoneutral condition. Whether a similar response is observed in humans is unconfirmed. Differences in skeletal muscle glucose uptake, and absorption at the gut combined with the previously mentioned differences in muscle recruitment patterns suggest that these fundamental limitations are driving the divergence in exogenous substrate utilization between cold and exercise.

While CHO ingestion has received a lot of attention, far less is known on the effects of lipid and protein feeding on cold endurance. The practice of ingesting protein and/or fat during cold exposure is one that has been employed by Northern inhabitants around the world for centuries (94, 95). It is only due to the modernization of these communities that a shift in macronutrient intake has been observed. Some have questioned whether these macronutrients were consciously chosen for their thermogenic properties or simply due to availability (100).

6.2. Thermogenic effects of feeding (TEF) and cold exposure

The thermogenic effect of protein ingestion has long been established and represents 20-30% of energy content (vs 0-3% for fat). This elevation in resting metabolic rate may last for several hours after ingestion in thermoneutral conditions (8). Whether this TEF can contribute to total heat production during prolonged cold exposure remains controversial. Beavers and Covino (116) found that ingesting 30 g of glycine during cold exposure (-18°C for 75 min, heavily clothed) increased the metabolic rate above values observed when ingesting 30 g of glucose, suggesting that the thermic effect of ingesting glycine was additive to shivering thermogenesis. In contrast a later study by Rochelle and Hovarth (117) showed that when semi-nude men, exposed to 7.5°C for 120 min, ingested either (1) 53.4 g of glucose, (2) 30 g of glycine with 22.1 g of glucose or (3) a 142-g steak heat production and oxygen consumption increased in parallel for all three conditions during the first 90 min. Rochelle and Hovarth (117) attributed this discrepancy to the colder stress imposed in their study compared to Beavers and Covino (116). The subsequent 30 min of cold exposure in Rochelle and Hovarth (117) provided further insight into a possible TEF during cold exposure such that heat production and oxygen consumption proceeded to stabilize in the glucose and steak conditions, while it continued to increase in the glycine condition. Further, authors observed that shivering was nearly negligible in the glycine meal, and lower in the steak meal than the glucose meal despite similar rates of heat production. This could indicate that the thermic effect of food may have a supplementary effect on whole body thermogenesis rather than the additive effect originally suggested by Beavers and Covino (116). In more recent studies conducted by Vallerand *et al.* (104, 106), participants ingested high-CHO energy bars containing ~30g CHO, ~4g fat, ~4 g protein and theobromine, a caffeine-like substance. They observed no significant changes in thermal responses compared to a control condition. They concluded that perhaps the TEF was masked by shivering thermogenesis when exposed to a cold condition eliciting an increase in metabolic rate of 2.5-3.5 X RMR. This further suggests that rather than adding to the heat production, TEF may simply be supplementing shivering thermogenesis, particularly at greater cold stresses where TEF may be indistinguishable. Clearly, the role that TEF plays in maintaining a thermal balance during compensable cold exposure needs to be investigated

7. CONCLUSIONS AND FUTURE DIRECTIONS

This review presented the metabolic requirements of shivering thermogenesis and described the effects of changes in energy reserves and nutritional status on the capacity to sustain this mode of heat production. Even though some new evidence indicates that nonshivering thermogenesis may play a greater role than previously thought in adult humans, shivering still provides the largest amount of heat during cold exposure. During shivering, muscle recruitment intensity and pattern (continuous vs. burst shivering) is highly variable between muscles and individuals having important repercussions on fuel

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selection but not thermogenic rate. It is suggested that this variability may be related partly to the neuromuscular characteristics of muscles. To better understand this issue, measurements of muscle fiber composition, fiber recruitment and fuel utilization will be needed in a range of subjects from highly aerobic marathon runners to highly anaerobic weight lifters. Previous work has also indicated that the types of substrates that can be used to sustain shivering are highly variable. Shivering can be sustained with widely different fuel for several hours under variable conditions of cold stress and CHO availability. Lipids are generally preferred during low intensity shivering while the role of CHO becomes more important as shivering intensity increases. Of the two sources of CHO, intramuscular glycogen provides most of the heat (75-80% of total CHO used) and the contribution of plasma glucose remains low. Yet, when CHO reserves are depleted, lipids and proteins oxidation rates are increased enough to compensate and sustain heat production. Under prolonged fasting in excess of 24h and energy deficit, little information is available on changes in substrate utilization. However, research suggests that prolonged energy deficit reduces the capacity to maintain heat production through shivering. Metabolic reasons are not yet well understood but clearly maintaining adequate food consumption in the cold is key for increasing survival odds. Most of the work on the consumption of food in the cold has focused on CHO assuming that the depletion of this food would reduce the capacity to sustain shivering. CHO consumption modifies slightly fuel selection by increasing CHO use. Using isotopic methods, researchers have shown that oxidation rates of ingested glucose remains low indicating that non-oxidative glucose disposable, mainly in the form of glycogen, is high. Mechanisms responsible for limiting in the oxidation rate of ingested glucose still need to be studied and the effects of lipid and protein ingestion need to be identified. Much work remains to fully understand the effects of food consumption in the cold. What, when and how much should cold exposed individuals eat? While some empirical evidence is available, little is known about the effects of dietary composition on cold endurance and modulations in shivering activity. Combining fundamental principles surrounding metabolic fuel selection with applied knowledge of human performance in the cold may allow important breakthroughs in this field of research.

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