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Human physiological responses to cold exposure: Acute responses and acclimatization to prolonged exposure

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ABSTRACT

Cold exposure in humans causes specific acute and chronic physiological responses. This paper will review both the acute and long-term physiological responses and external factors that impact these physiological responses. Acute physiological responses to cold exposure include cutaneous vasoconstriction and shivering thermogenesis which, respectively, decrease heat loss and increase metabolic heat production. Vasoconstriction is elicited through reflex and local cooling. In combination, vasoconstriction and shivering operate to maintain thermal balance when the body is losing heat. Factors (anthropometry, sex, race, fitness, thermoregulatory fatigue) that influence the acute physiological responses to cold exposure are also reviewed. The physiological responses to chronic cold exposure, also known as cold acclimation/acclimatization, are also presented. Three primary patterns of cold acclimatization have been observed, a) habituation, b) metabolic adjustment, and c) insulative adjustment. Habituation is characterized by physiological adjustments in which the response is attenuated compared to an unacclimatized state. Metabolic acclimatization is characterized by an increased thermogenesis, whereas insulative acclimatization is characterized by enhancing the mechanisms that conserve body heat. The pattern of acclimatization is dependent on changes in skin and core temperature and the exposure duration.
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Contents

1. Introduction

Human beings work and play in many cold-weather environments (low temperature, high winds, low solar radiation, rain/water exposure), and cold stress is rarely a limiting factor. For the most part, human beings utilize behavioral thermoregulation in the cold. These

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behaviors include migration, building shelter, wearing high-insulation clothing, and physical activity, and David Bass, the noted environmental physiologist, once stated that "man in the cold is not necessarily a cold man." (Bass, 1958). However, there are situations where these behaviors are not adequate, and physiological responses are required to maintain thermal balance and protect against cold-weather injury. Furthermore, there are also scenarios where chronic cold exposure is experienced and adaptations occur. This paper will review human physiological responses to cold, focusing on both acute and long-term responses that cause cold acclimatization.

2. Biophysics of cold exposure

Changes in core temperature are caused by either a positive or negative change in heat storage. If the body produces more heat than it dissipates, body tissue storage is positive, and deep body temperature rises. Conversely, if heat production is less than that lost to the external environment, then heat storage will be negative and deep body temperature will fall. We can present these relationships between production and loss mathematically as follows (Gagge and Gonzalez, 1996):

$$S = M - (+\text{Work}) - E \pm R \pm C \pm K \cdot s$$

where: S = heat storage, M = metabolic heat production, E = evaporation, R = radiation, C = convection, and K = conduction. Positive numbers indicate heat gain and negative values, heat loss. E, R, C, and K are the heat exchange pathways (Gonzalez and Sawka, 1988). All units are in $W \cdot m^{-2}$. When environmental temperature and water vapor pressure are lower than the skin temperature and vapor pressure of water at the skin, heat loss results.

Humans cool two to five times more quickly during immersion in cold water, compared to when they are exposed to air at the same temperature (Hong, 1984); this is due to higher conductive and convective heat loss in water. This is further demonstrated by comparing the temperatures where humans remain in heat balance or thermoneutral conditions. In water, the thermoneutral temperature is about 35 °C (Costill et al., 1967; Craig and Dvorak, 1966). In comparison heat balance is achieved during air exposure at an ambient temperature of about 26 °C (Craig and Dvorak, 1966). Therefore, a resting person will be unable to maintain their deep body temperature when immersed in water at a temperature regarded as thermoneutral in air. The reason for these differences lies in the physical properties of air and water; the thermal conductivity of water is 25 times that of air (Toner and McArdle, 1996). Therefore cooling is extremely effective, even in moderately cool water and results in rapid dissipation of the heat which is delivered to the skin by conduction and convection (blood circulation) from the deeper tissues.

3. Acute physiological responses

A decrease in peripheral temperatures, primarily skin, and core temperature elicits the primary cold thermoregulatory responses (vasoconstriction and shivering), also called thermoeffector responses. For example, afferent signals from the skin are sensed in the preoptic area of the anterior hypothalamus, from which efferent signals arise causing cutaneous vasoconstriction and/or shivering thermogenesis. The control of these efferent responses during changing mean body temperature (integration of core and skin temperature) is depicted in Fig. 1. The threshold is defined as the temperature point where the effector response is initially activated, whereas the sensitivity of the response is denoted by the slope of the mean body temperature-effector response.

Upon cold exposure, the initial physiological response is a peripheral skin vasoconstriction and a reduction in skin blood flow. This reduces convective heat transfer between the body's core and shell (skin, subcutaneous fat, and skeletal muscle), effectively increasing insulation by the body's shell. However, heat is still lost from the exposed body surface faster than it is replaced; therefore, skin temperature declines. Vasoconstriction begins when skin temperature falls below about 35 °C and becomes maximal when skin temperature is 31 °C or less (Veicsteinas et al., 1982). Thus, the vasoconstrictor response to cold exposure helps retard heat loss and defend core temperature but at the expense of a decline in peripheral tissue temperature.

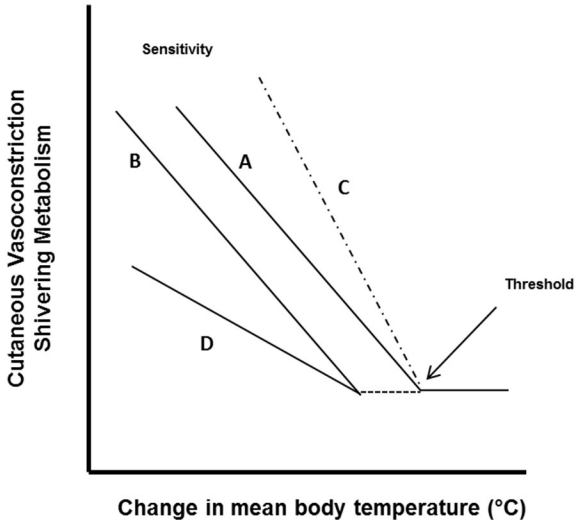

Fig. 1. Representation of the thermal effector response (vasoconstriction, shivering) to a change in mean body temperature (ΔMBT) relationship. As mean body temperature decreases a thermal effector response is elicited and increases (line A). The inflection point where this increase occurs is the threshold. The slope of the effector-ΔMBT relationship represents the sensitivity of the response. Line B denotes a response where the threshold is shifted, such that a thermal effector response does not occur until a larger ΔMBT occurs. In Line C, there is no threshold shift, but a change in the sensitivity of the response. For this example, line C denotes a greater sensitivity to a ΔMBT, that is, there is a greater effector for a given ΔMBT. Line D denotes both a threshold and sensitivity change.

There are three primary ways that vasoconstriction occurs (reflex and local cooling and a decrease in deep body temperature), each with separate physiological mechanisms. This review will focus on the skin temperature responses as these are most common. The first is a reflex response, caused with whole-body cooling, or when one area of the body is cooled, causing other areas to reflexively vasoconstrict (e.g., face cooling elicits a reflex vasoconstriction to the fingers (Brown et al., 2003)). The afferent and efferent neural pathways for reflex vasoconstriction have been determined (see Morrison paper in this series, Figure XX – will be added by journal). Cold exposure on the skin triggers a receptor-mediated neural signaling pathway that traverses through the dorsal horn of the spinal cord to the lateral brachial nucleus and then on to the preoptic area of the hypothalamus, with efferent signals travelling from the brain through the interomediolateral cell column of the spinal cord and to sympathetic nerves innervating cutaneous blood vessels. Norepinephrine is the primary neurotransmitter that accounts for ~60% of the reflex cold-induced vasoconstriction in skin vasculature (Charkoudian, 2010), while neuropeptide Y is responsible for ~20–30% (Stephens et al., 2001, 2004).

Vasoconstriction is also caused by local cooling of skin blood vessels. Early in the local cooling response (first 10 min with no reflex cooling occurring from other areas), vasoconstriction is primarily mediated by norepinephrine and the α_2-adrenergic receptor (Thompson-Torgerson et al., 2008). However as cooling continues, non-adrenergic and non-neuronal mechanisms are responsible for the reduction in cutaneous blood flow. Skin cooling results in an increase in mitochondrial reactive oxygen species, which causes an increase in Rho kinase (Thompson-Torgerson et al., 2007a, 2007b, 2008). Increased Rho kinase causes an inhibition of myosin light chain phosphatase allowing the myosin light chain to be phosphorylated leading to cutaneous vasoconstriction. As well, local cooling

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induced increases in Rho kinase causes a translocation of α_{2C} receptors from the Golgi to the plasma membrane enhancing α_2 receptor sensitivity to norepinephrine (Chotani et al., 2000, 2004; Johnson, 2007). Fig. 2 schematically presents the mechanisms responsible for cutaneous vasoconstriction following local cold exposure. Increases in RhoA/Rho kinase also lead to a decrease in nitric oxide by down-regulating endothelial nitric oxide synthase (Thompson-Torgerson et al., 2008).

Cold signals are transduced through the transient receptor potential melastatin 8 (TRPM8) receptor. This receptor is a temperature sensitive, calcium-permeable, cationic ion channel that also responds to chemical stimuli such as menthol (Johnson et al., 2009). It is found in the dorsal root ganglion sensory neurons that innervate the skin and also in trigeminal ganglion sensory neurons (Wang and Siemens, 2015) and is expressed in vascular smooth muscle (Johnson et al., 2009). Fig. 3 presents the molecular mechanisms that cause a physiological response upon cold exposure. Pharmacologically blocking the TRPM8 receptors deleteriously impacts autonomic responses to cold exposure. Almeida et al. (Almeida et al., 2012) found that in wild-type mice, use of the TRPM8 receptor blocker M8-B caused a decline in core body temperature. This change in core temperature was caused by both an attenuated vasoconstrictor and thermogenic response, leading to greater heat loss and a decline in metabolic heat production, respectively.

Cold-induced vasoconstriction has pronounced effects in acral skin regions (e.g., fingers, toes) making them particularly susceptible to cold injury and loss of manual dexterity (Brajkovic et al., 1998). In these areas, another vasomotor response, cold-induced vasodilation (CIVD), modulates the effects of vasoconstriction. First described by Lewis and also known as the hunting reflex (Lewis, 1930), CIVD is a periodic fluctuation of blood flow and skin temperature following an initial decline in these variables during cold exposure. A similar cold-induced vasodilation in the forearm appears to reflect vasodilation of muscle as well as cutaneous vasculature (Ducharme et al., 1991a). Originally thought to just be a local cooling effect, evidence suggests that a central nervous system mechanism mediates CIVD (Lindblad et al., 1990). CIVD responses are more pronounced when the body core and skin temperatures are warm (hyperthermic state) and suppressed when they are cold (hypothermic state), when compared to normothermia (Daanen and Ducharme, 1999; Daanen et al., 1997; O'Brien et al., 2000). Exercise training (50% peak power; 5 days·week-1; 4 weeks) may also improve the CIVD response (Keramidas et al., 2010).

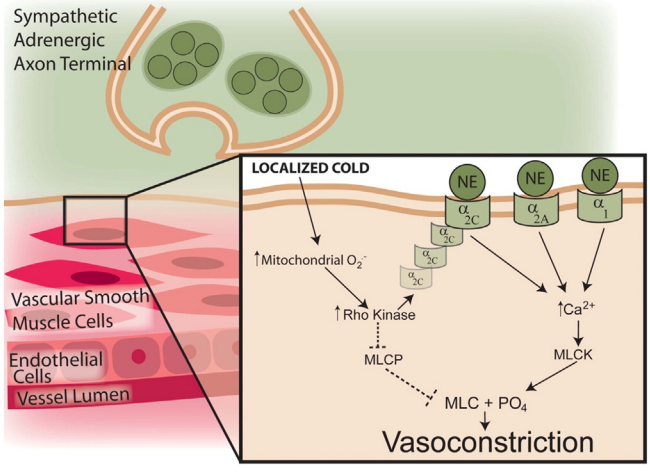

Fig. 2. Representation of the mechanisms involved in vasoconstriction following local cold exposure. Local cooling of cutaneous blood vessels causes an increase in reactive oxygen species (O_2^-) within the mitochondria. This in turn activates RhoA and Rho kinase, which can induce vasoconstriction through 2 pathways. In pathway 1, Rho kinase causes translocation of alpha-2_C adrenoceptors ($\alpha 2_c$) receptors to move from the Golgi to the plasma membrane. These $\alpha 2_c$ receptors bind norepinephrine (NE), leading to calcium (Ca^{2+}) influx and phosphorylation of myosin light chain (MLC) by the MLC kinase. In the second pathway, increased Rho kinase inhibits myosin light chain phosphatase, which allows MLC to remain phosphorylated and cutaneous blood vessels to remain constricted. Printed with permission from Thompson-Torgerson et al. (2008).

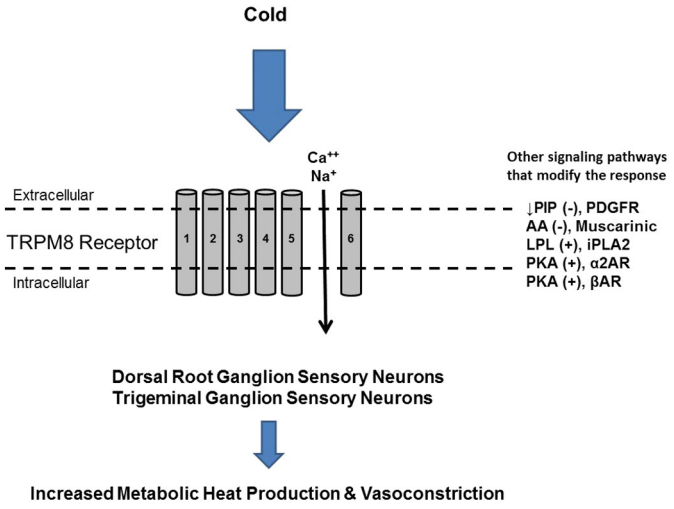

Fig. 3. Representation of cold signal transduction through the transient potential melastatin 8 (TRPM8) receptor, eliciting a downstream increase in metabolic heat production and vasoconstriction. The response is modifiable by other signaling pathways. PIP_2, phosphatidylinositol bisphosphate; PDGFR, platelet-derived growth factor receptor; AA, arachidonic acid; LPL, lysophospholipids; iPLA2, Ca^{2+}-independent subtype of phospholipase A2; PKA, protein kinase A; α_2 AR, alpha-2 adrenergic receptor; PKA, protein kinase A; βAR, beta-adrenergic receptor.

Cold exposure also elicits increased metabolic heat production in humans, which can help offset heat loss. In humans, most cold-induced thermogenesis is attributable to skeletal muscle contractile activity. Humans initiate this thermogenesis by voluntarily modifying behavior, that is, increasing physical activity (e.g., exercise, increased fidgeting) or by shivering. Shivering, which consists of involuntary repeated rhythmic muscle contractions during which most of the metabolic energy expended is liberated as heat and little external work is performed, may start immediately or after several minutes of cold exposure, and is initiated by a decrease in skin temperature. The fall in core temperature provides the greatest stimulus for shivering, with the ratio of the T_{core}/T_{skin} contribution to shivering being 3.6:1 (Frank et al., 1999). Shivering becomes maximal at a core temperature of ~34–35 °C and ceases at ~31 °C (Castellani et al., 2006). Shivering usually begins in the torso muscles, then spreads to the limbs (Bell et al., 1992). The intensity and extent of shivering vary according to the severity of cold stress (e.g., air or water exposure, change in core temperature). As shivering intensity increases and more muscles are recruited to shiver, whole-body metabolic rate increases, typically reaching about 200–250 W during resting exposure to cold air but often exceeding 350 W during resting immersion in cold water. Shivering metabolism as high as 763 W has been recorded during immersion in 12 °C water (Golden et al., 1979).

It has been well established that rodents increase metabolic heat production in brown adipose tissue (BAT) in response to cold exposure, and it was thought for many years that adult humans lacked this mechanism. However a series of papers (Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009) using positron emission tomography (PET) and computed tomography (CT) scans along with the tracer 18F-fluorodeoxyglucose has discovered that adult humans do indeed have active BAT that becomes active upon cold exposure. Highest BAT levels are found in the neck, supraclavicular tissue, and thoracic and abdominal paraspinal sites (Cypess et al., 2009). BAT activation is negatively correlated with body mass index and % body fat (Saito et al., 2009; van Marken Lichtenbelt et al., 2009) and women appear to have more BAT than men (Cypess et al., 2009). However there is no evidence that BAT thermogenesis can increase high enough

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to defend core temperature during acute whole body cold exposures that require a robust metabolic response.

3.1. Modifiers of thermoregulatory effector responses to cold

Individual characteristics are the primary source of variability in the physiological response to cold exposure. Primary among these characteristics is body anthropometry, but other sources of individual differences include sex, age, and prior cold/exercise fatigue.

3.2. Anthropometry/Body Composition

Most variability between individuals in their thermoregulatory responses and capability to maintain normal body temperature during cold exposure is attributable to anthropometric and body composition differences. Large individuals lose more body heat in the cold than smaller individuals because they have larger body surface areas. In general, persons with a large ratio of surface area to mass have greater declines in body temperature during cold exposure than those with a smaller ratio (Gagge and Gonzalez, 1996; Toner and McArdle, 1996). All body tissues provide thermal resistance to heat conduction (i.e., insulation) from within the body. In resting individuals, unperfused muscle tissue provides a significant contribution to the body's total insulation (Ducharme et al., 1991b). However, during exercise or other physical activity that contribution declines because increased blood flow through muscles facilitates convective heat transfer from core to the body's shell. Fat has the highest thermal resistivity of all the body's tissues. Therefore, individuals with high subcutaneous fat levels are protected against heat loss and subsequent declines in core temperature, and the fall in core temperature during cold exposure is inversely related to subcutaneous fat thickness (Toner and McArdle, 1996). The mechanism for this protective effect of subcutaneous fat thickness is primarily a biophysical one. More subcutaneous fat, hence more insulation, reduces conductive heat loss from underlying tissue. Thus skin temperature falls more as subcutaneous fat thickness increases. A reduced skin temperature lowers the thermal gradient between skin and the ambient environment, and since the rate of body heat loss depends on the magnitude of that gradient, a lower skin temperature effectively lowers whole body heat loss and attenuates the fall in core temperature (Buskirk et al., 1963; Cannon and Keatinge, 1960).

3.3. Sex

Sex-associated differences in thermoregulatory responses and thermal balance during whole-body cold exposure appear almost entirely attributable to anthropometric and body composition characteristics (Toner and McArdle, 1996), as shivering sensitivity (Glickman-Weiss et al., 2000a, 2000b) are similar between men and women. For example, in men and women having equivalent total body masses, surface areas are similar, but the women typically have a greater fat content which enhances insulation. However, in women and men of equivalent subcutaneous fat thickness, the women have a greater surface area but smaller total body mass (and lower total body heat content) than men. Thus, while insulation is equivalent, total heat loss during resting cold exposure would be greater in the women, because they have a larger surface area for convective heat flux, and body temperature would tend to fall more rapidly for any given thermal gradient, unless shivering thermogenesis compensated with a more pronounced increment than in the men. This compensation may be possible when heat flux is low (mild cold conditions), but women's smaller lean body mass limits their maximal capacity for thermogenic response; therefore, a more rapid core temperature decline might occur under severely cold conditions than in men of comparable body mass (McArdle et al., 1984a, 1984b). However, during exercise in cold-water, men and women who have equivalent body fat percentages exhibit similar thermoregulatory responses, due to the women having a more favorable fat distribution over the exercising limbs, compared to the men (McArdle et al., 1984b).

Peripheral responses to cold exposure are different between women and men. Bartelink et al. (1993) observed during local cold exposure that women had a lower finger skin temperature and blood perfusion compared to men and this persisted into recovery. These findings correlate with clinical observations that demonstrate that women have a higher incidence of Raynaud's phenomenon (Grisanti, 1990). Mechanistically, this may be related to estrogen increasing expression of cold-sensitive α_{2C}-adrenoceptors (Eid et al., 2007).

The thermoeffector responses to cold vary within a women's menstrual cycle. During the luteal phase, the sensitivity of the shivering response is lower, compared to the follicular phase, i.e., the slope of the mean body temperature-metabolic heat production relationship is attenuated (Gonzalez and Blanchard, 1998). Furthermore, there are differences in finger skin temperature and cutaneous blood flow within a menstrual cycle following finger cooling, with the lowest values observed during the mid-luteal phase, compared to the pre-ovulatory period (Bartelink et al., 1990). Oral contraceptive use also affects the thermoregulatory effector responses to cold exposure. Charkoudian and Johnson Charkoudian and Johnson (1999) found that skin vasoconstriction occurred at a higher core temperature during the high hormone phase of oral contraceptive use (elevated estrogen and progestin), compared to the low-hormone phase. Changes in reproductive hormone levels caused by oral contraceptive use also impact the neurotransmitters that modulate reflex vasoconstriction. During the high hormone phase of oral contraceptive use, there is a non-adrenergic component, likely another sympathetic co-transmitter, responsible for reflex vasoconstriction (up to 40%), in addition to the alpha-adrenergic mediated vasoconstriction (Stephens et al., 2002). However, this non-adrenergic component was absent during the low reproductive phase of contraceptive use. Although it has never been definitively demonstrated, it is likely this non-adrenergic sympathetic co-transmitter is neuropepetide Y (NPY) (Stephens et al., 2004). In contrast to women taking contraceptives, normally menstruating women do not exhibit a difference in the neurotransmitters modulating cutaneous vasoconstriction during high- (luteal phase) and low-hormone (follicular) status (Thompson and Kenney, 2004).

3.4. Age

People who are older than 60 years may be less cold tolerant than younger persons, due to reduced vasoconstriction and heat conservation in comparison to their younger counterparts (DeGroot and Kenney, 2007; Falk et al., 1994; Frank et al., 2000; Kenney and Armstrong, 1996; Smolander, 2002; Young and Lee, 1997). As shown earlier, NE and NPY are the primary sympathetic neurotransmitters responsible for reflex vasoconstriction in the young. However, in the elderly, the co-transmitter NPY does not mediate vasoconstriction. Furthermore, NE-mediated vasoconstriction is attenuated with aging, likely through a decrease in synthesis or release of that neurotransmitter (Holowatz et al., 2010). In addition, the skin vasculature does not respond as robustly to exogenous administration of NE, (Thompson and Kenney, 2004), suggesting a blunted end-organ responsiveness (Holowatz et al., 2010).

Local cold induced vasoconstriction of cutaneous arteries, through alpha-adrenergic and Rho kinase/Rho, changes with aging. Compared to younger individuals, there is a shift away from an adrenergic response (NE) to a non-adrenergic mechanism, i.e., Rho kinase. However, despite this shift in the mechanism, there is no change in the overall vasoconstrictor response to local cooling (Thompson et al., 2005; Thompson-Torgerson et al., 2007b).

People generally experience a decline in physical fitness with aging. If older people exercise at the same absolute metabolic rates as younger individuals, the older person will be working at a higher $\%VO_{2max}$, and will fatigue sooner. Fatigue leads to a decrease in absolute heat production increasing the likelihood of a reduction in core temperature. Older

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individuals also appear to have a blunted thermal sensitivity to cold. For example, in studies where subjects have control of setting a thermostat as the ambient temperature fluctuates, older individuals will allow the air temperature to fall to lower levels before *re*-adjusting the thermostat (Ohnaka et al., 1993; Taylor et al., 1995). Aging also appears to reduce the deep body temperature threshold for the onset of shivering and cutaneous vasoconstriction (Frank et al., 2000). Collectively, the age-related changes could increase susceptibility to hypothermia in older persons.

Children, in comparison to adults, typically have a higher body surface area-to-mass ratio and lower subcutaneous fat amounts and this leads to substantial falls in core temperature when swimming in cold (20 °C, 68 °F) water (Sloan and Keatinge, 1973). Interestingly, in 11–12 year old boys who had similar amounts of subcutaneous fat as adult men (19–34 years), core temperature was the same in 5 °C air both at rest and during exercise, but the mechanism for achieving this was different. The boys exhibited a more pronounced vasoconstrictor and metabolic response compared to the men (Smolander et al., 1992). Pre-menarcheal girls do not defend core temperature as well as eumenorrheic girls during exercise-cold stress, due to a diminished vasoconstrictor response (Klentrou et al., 2004).

3.5. Exertional fatigue

An association between exertional fatigue and susceptibility to hypothermia was first reported by Pugh (1966, 1967). He analyzed reports of 23 separate occasions that had led to numerous cases of hypothermia and 25 deaths. In his analysis of these incidences, Pugh identified physical exhaustion as a contributing factor for hypothermia. More recently exhaustion and hypothermia were again linked as causal factors for a large number of serious hypothermia casualties and four deaths during cold exposure following a grueling 60-day military training course in which soldiers are underfed, sleep deprived, and physically exhausted (Young et al., 1998). Degraded thermoregulatory effector responses (shivering and vasoconstriction) during/following physical exertion may potentially increase the risk of hypothermia. This degraded effector response was termed "thermoregulatory fatigue" (Castellani et al., 1999).

Shivering fatigue has been documented in two studies. Quantitative evidence for shivering fatigue was reported by Bell et al. (1992). They found that over a 2-h resting exposure to 10 °C air, the central frequency of the EMG recording in the shivering pectoralis major decreased with time, suggesting fatigue of this muscle group. Thompson and Hayward (Thompson and Hayward, 1996) reported that during a 5-h walk at a constant pace in cold, rainy conditions, one participant maintained a stable metabolic rate and deep body temperature for the first three hours of exposure, but then exhibited a progressive decline in metabolic rate and deep body temperature over the final 2 h, despite the fact that walking pace remained unchanged throughout (Thompson and Hayward, 1996). Another important factor to consider is that shivering may be blunted due to hypoglycemia. Two studies clearly show that very low glucose levels (< ~ 3 mM) impair metabolic heat production (Gale et al., 1981; Passias et al., 1996), with the effect most likely centrally-mediated (Gale et al., 1981).

Follow-up studies were conducted to specifically examine if thermoregulatory fatigue would occur in different scenarios, including multi-stressor (physical exhaustion, underfeeding, sleep loss) and multiple cold-water immersion. In the multiple-stressor studies, shivering responses were found to be delayed during a cold-exposure trial performed immediately after completing either an exhaustive 9-week training course (Young et al., 1998) or 84-h of exertional fatigue, negative energy balance and sleep loss (Castellani et al., 2003). Fig. 4 shows the mean body temperature-metabolic heat production response before and after the 84-h multi-stress period, clearly demonstrating a shift in the onset/threshold of shivering thermogenesis.

The multiple stressor studies provided insight into possible mechanisms of shivering fatigue, but did not directly answer the question of whether a muscle that is shivering for long durations fatigues. To determine whether shivering responses to cold exhibited fatigue, metabolic heat production was measured during 2-h cold-water immersions (20 °C) repeated three times, serially in a single day (2-hour rewarming intervening). Those shivering responses were then compared to metabolic heat production measured during a single immersion completed at the same time of day (Castellani et al., 1998). Cold-water immersion produces more rapid core and peripheral cooling and induces higher shivering rates than cold air, potentially causing fatigue. Similar to the findings in the multi-stressor studies, metabolic heat production was lower during the serial immersions (REPEAT), than when only a single immersion was completed at that same time of day (CONTROL). The blunted thermogenic response in REPEAT appeared to be due to a delay in the shivering onset, i.e. the intercept for the mean body temperature-change in metabolic heat production relationship shifted such that the increase in metabolic heat production during the 1100 and 1500 REPEAT exposures was not observed until the subjects achieved a lower mean body temperature. These data, like the shift in shivering onset observed in the multiple stressor studies suggests a centrally-mediated change in the recruitment of muscle for shivering thermogenesis, and a greater susceptibility to hypothermia.

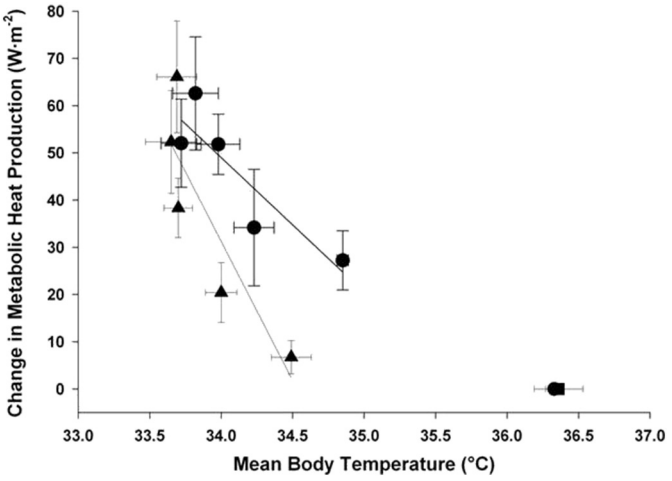

Fig. 4. Metabolic heat production vs. mean body temperature during sedentary exposure to 10 °C air following 84-h of exertional fatigue, sleep deprivation, and negative energy balance (SUSOPS) vs. rested conditions (Control). SUSOPS demonstrated a significant shift for the onset of shivering thermogenesis. From Castellani et al. (Cannon and Keatinge, 1960).

Follow-on work examined the role of both acute and chronic exercise, without the accompanying stressors of underfeeding and sleep loss. These studies found that the vasoconstrictor responses to cold exposure were blunted following a short bout (Castellani et al., 1999) or several days (Castellani et al., 2001) of exercise.

4. Physiological adjustments to prolonged or repeated cold exposure

Humans chronically exposed to cold, either prolonged cold-exposure periods or a series of repeated, intermittent cold-exposure periods, experience adjustments[1] in the physiological responses to cold compared to responses exhibited during acute or initial cold exposure. Chronic heat exposure induces a fairly uniform pattern of physiological adjustments in humans that provide a distinct thermoregulatory advantage in terms of protecting from heat injury/illness and preserving physical performance capability. In contrast, depending on the specific

[1] The changes in physiological responses experienced by an individual as a result of chronic or repeated cold exposures are properly termed *adjustments*. The differences in physiological responses to cold exhibited by people in population groups who have lived in cold climates for many generations as compared to people from population groups living in warm climate, are termed *adaptations*.

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conditions experienced and the degree to which thermal balance is disrupted, chronic cold exposure can produce three different patterns of physiological adjustments: 1) habituation, 2) metabolic adjustments, and 3) insulative adjustments. These three patterns vary considerably, both qualitatively in terms of the specific nature of the physiological adjustments developed, and quantitatively in terms of the thermoregulatory advantages conferred by those adjustments. Further, whereas chronic heat stress typically involves whole-body heating, and the resulting adjustments produced usually affect the whole-body response, cold-exposure can often involve cooling of very limited regions of the body (e.g., the fingers or nose), while the remainder of the body (i.e. skin surface and deep body core) are protected from the environmental stress and do not experience significant cooling. Thus, local or regional adjustments in physiological responses may be more readily experienced with chronic cold exposure than with chronic heat exposure. Therefore, the remainder of this paper will review the physiological characteristics of different patterns of adjustments exhibited by humans chronically exposed to cold, and consider the underlying mechanisms thought responsible for their development.

4.1. Habituation

The most commonly observed pattern of thermoregulatory adjustments observed in response to chronic or repeated cold exposure is habituation. As habituation develops, physiological responses to cold become less pronounced (blunted shivering, blunted cutaneous vasoconstrictor response or both) than in the unacclimatized state (Young, 1996). Indigenous circumpolar residents such as the Inuits (Andersen et al., 1960; Hart et al., 1962; Hildes, 1963), other Native North Americans from the Arctic (Elsner et al., 1960; Irving et al., 1960) and Norwegian Saami (Andersen et al., 1960) appear to respond to whole-body cold exposure in the same general manner as persons indigenous to temperate climates, that is metabolic heat production increases due to shivering, and skin temperature and peripheral heat loss decrease due to vasoconstriction of peripheral blood vessels. However, when compared to people from temperate climates, the increase in metabolic heat production associated with shivering (as reflected by the increase in VO_2) and the vasoconstriction of peripheral blood vessels (as reflected by the decline in skin temperature) appear less pronounced in circumpolar residents, as demonstrated in studies of Norwegian Saami shown in Fig. 5 (Andersen et al., 1963).

Habituation can be produced even if cold exposure is limited to relatively small regions of the body as opposed to whole-body exposures. For example, fishermen and fish filleters work long hours every day with one or both hands immersed in cold water, and these people have been shown to maintain higher finger and hand temperatures and lower systemic blood pressures during hand immersion in cold water compared to control subjects (LeBlanc, 1988; LeBlanc et al., 1960; Nelms and Soper, 1962). Slaughterhouse workers who handle cold meat tend to show similar effects, although the effects are not as pronounced (Enander et al., 1980). This suggests that repeated localized cold exposure can produce localized habituation of vasoconstrictor responses. There is also evidence that repeated localized cold exposures can induce habituation of the whole-body vasoconstrictor response to cold (Savourey et al., 1996).

Genetic adaptations could conceivably account for differences in the shivering and vasoconstrictor responses to cold observed in cross-sectional comparisons of people indigenous to circumpolar regions and people from temperate conditions, and in comparisons of people from different occupations. However, longitudinal acclimatization studies have shown that habituation can also be induced in varying degrees in people from temperate climate regions who experience repeated, intermittent periods of cold exposure (Armstrong and Thomas, 1991; Hesslink et al., 1992; Marino et al., 1998; Mathew et al., 1981; Silami-Garcia and Haymes, 1989). The variation in the degree of habituation developed in response to cold exposure appears related to the severity

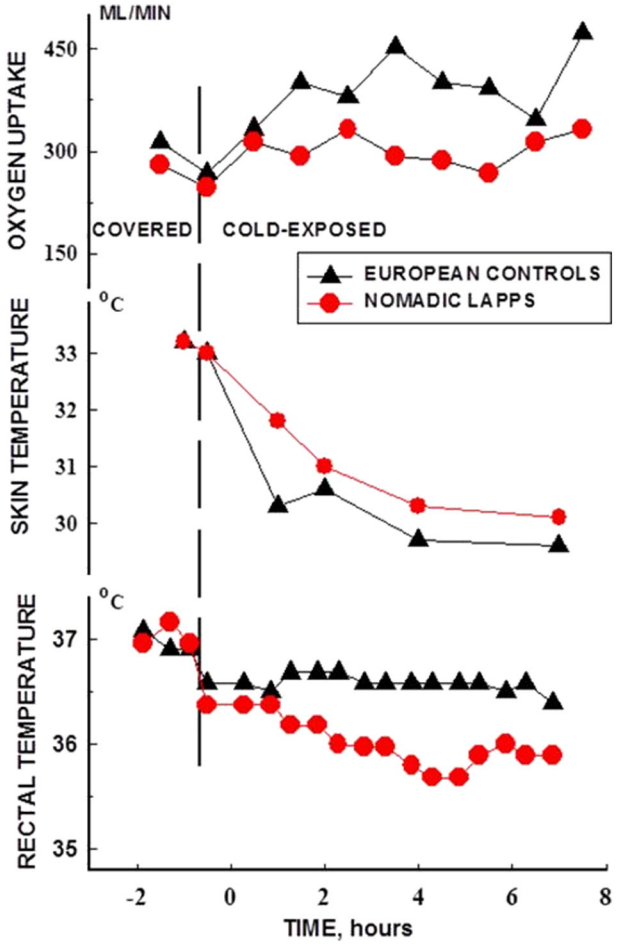

Fig. 5. Oxygen uptake, and skin and rectal temperature responses during an overnight cold exposure (0 °C) between Norwegain Saami and European controls. Data demonstrate a cold habituation response, i.e., thermal effector responses are blunted (lower metabolic heat production, less vasoconstriction) in the indigenous circumpolar residents. Drawn from data reported by Andersen et al. (Andersen et al., 1960).

of stress, i.e., duration of cold exposure, suggesting that physiological mechanisms rather than genetic adaptations are responsible for development of habituation. For example, in studies acclimating subjects to fairly brief cold exposures, habituation effects are usually limited to blunting of shivering (Armstrong and Thomas, 1991; Hesslink et al., 1992; Silami-Garcia and Haymes, 1989), whereas in studies employing longer exposure durations and/or a longer acclimatization periods, more pronounced habituation of both shivering and vasoconstrictor responses to cold are seen (Marino et al., 1998; Mathew et al., 1981). The blunting of shivering and vasoconstrictor responses that develop with habituation, whether produced by living in cold climates or by acclimating to repeated, intermittent cold exposure, can be sufficiently pronounced so as to allow a greater fall in core temperature during cold exposure than experienced by non-habituated people (i.e., a *hypothermic* pattern of habituation, as shown in the responses of the Saami shown in Fig. 1) (Andersen et al., 1960; Davis, 1961; Keatinge, 1961; Kreider et al., 1959; Marino et al., 1998). Data also suggest that increased physical fitness may also blunt the vasoconstrictor response as evidenced by higher overall mean skin and peripheral temperatures (Adams and Heberling, 1958; Heberling and Adams, 1961). The specific physiological mechanisms underlying the blunting of shivering and vasoconstrictor responses to cold are not clearly defined, but some studies provide evidence suggesting that following chronic or repeated cold exposures, habituation is accompanied by reduced sympathetic nervous activation and enhanced parasympathetic activation during exposure to cold (Harinath et al., 2005; Makinen et al., 2008). For example,

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Leppaluoto et al. (Leppäluoto et al., 2001) demonstrated after 11 days of cold air exposure (2 h·d^{-1}; 10 °C), the norepinephrine response to cold was reduced by 20%.

4.2. Metabolic Acclimatization

Some researchers have suggested that chronic cold exposures can result in development of a more pronounced thermogenic response to cold (Young, 1996). This pattern of cold adjustment has been termed metabolic acclimatization. Either exaggerated shivering or development of nonshivering thermogenesis could account for a more pronounced thermogenic response to cold during metabolic acclimatization.

Circumpolar residents (e.g., Alaskan Inuits and other Native Americans) reportedly maintain higher resting metabolic rates than subjects from temperate climates, enabling them to maintain warmer skin temperatures with less shivering during cold exposure (Young, 1996). However, the increased metabolic rate of circumpolar residents was also apparent in warm conditions, not just during cold exposures, suggesting that this adjustment was not specific to chronic cold exposure, but perhaps attributable to other factors such as diet (Leonard et al., 2014; Leonard et al., 2002; Rennie et al., 1962; Rodahl, 1952; Snodgrass et al., 2005). Similarly increased metabolic rates during cold exposures were observed by Hammel (1960) in Alacaluf people compared to unacclimatized European subjects. The Alacaluf were nomadic Native Americans who at the time that Hammel did these studies (Hammel, 1960) were living in fairly primitive conditions (unheated dwellings and minimal clothing) on coastal islands off the southern tip of South America in constantly rainy and cold weather, but here again, whether the higher metabolic rate of the Alacaluf was really an adjustment to chronic cold exposure or the effects of diet and lifestyle cannot be determined. Finally, the Ama diving women of Korea, reportedly experienced a substantial increase in basal metabolic rate between summer and winter (Kang et al., 1963). At the time that these studies were conducted, the Ama divers dove daily without protective wet suits in water ranging in temperature from 27 °C in summer to as low as 10 °C in winter (Kang et al., 1963). Non-diving women from the same communities as the diving women were observed to maintain a constant basal metabolic rate throughout the year, strongly suggesting the seasonal elevation in metabolic rate of diving women was an effect of chronic cold, and not an effect of diet or other lifestyle factors (Kang et al., 1963). Regardless of what stimulated these adjustments, there was no apparent thermoregulatory benefit of the higher basal metabolic rates. For example, the body temperatures of the Ama women fell much lower during winter diving and they were unable to continue working as long compared to summer diving (Kang et al., 1963).

Those aforementioned studies all employed cross-sectional comparisons of persons chronically exposed to cold to control subjects lacking that chronic cold-exposure experience, making it difficult to determine whether differences observed reflect the effects of chronic cold or other factors. However, there have also been some longitudinal studies (i.e., employing subjects repeatedly measured throughout a series of cold exposures) suggesting that a metabolic pattern of cold acclimatization can develop in people who normally live in temperate climates. In one of the oldest and most often cited such studies, Davis (1961) reported that men who were acclimatized for 31 days by spending eight hours per day exposed in a chamber to mild cold air (12 °C) conditions, demonstrated an enhanced non-shivering thermogenesis in response to cold exposure. Davis observed that (see upper panel of Fig. 6), while both metabolic heat production (measured by open-circuit respirometry) and shivering intensity (measured from EMG activity of the upper arm and thigh) during cold exposure declined over the course of the cold acclimatization program, the decrease in shivering (EMG activity) appeared to be more pronounced than the decrease in metabolic heat production, therefore he concluded that non-shivering thermogenesis must have developed to offset the decline in shivering. However, when Davis' data are replotted (see lower panel of Fig. 6), it can be seen that, in fact, the decline in metabolic heat production during cold acclimatization was, in fact, closely correlated with the decline in shivering EMG activity. Further, the assumption that decreases in the EMG activity of the arm and thigh muscles are representative of a decline in whole-body shivering is probably unjustified, since shivering activity of other muscle groups could have increased. Thus, the findings reported by Davis (1961) should not be interpreted as conclusively demonstrating development of non-shivering thermogenesis during cold acclimatization.

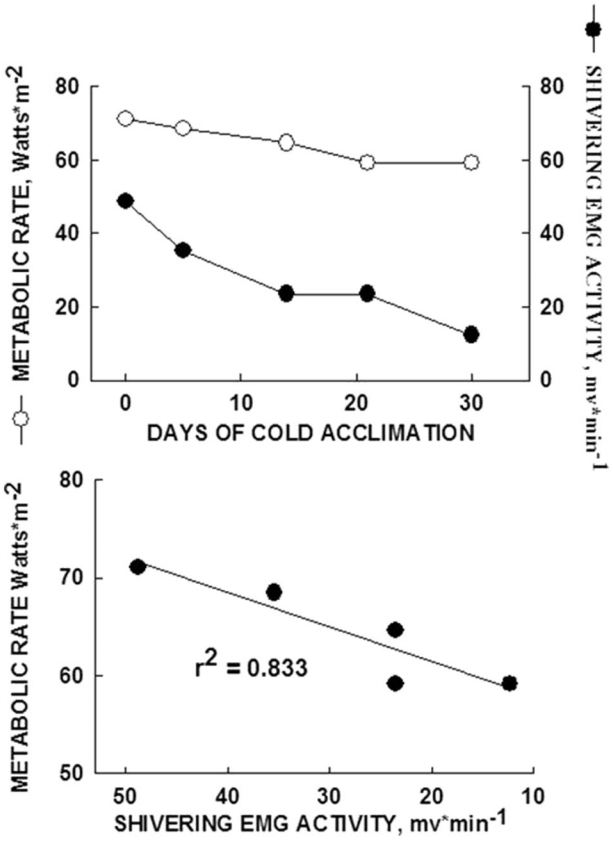

Fig. 6. Effect of 31 days of cold acclimatization on the metabolic and shivering electromyogram (EMG) responses (Davis, 1961). Top panel shows that over the course of acclimatization, the decrease in shivering activity was greater than the decline in metabolic rate, which was interpreted as an enhancement of non-shivering thermogenesis. However, when Davis' data are replotted (lower panel), the decline in metabolic heat production during cold acclimatization was closely correlated with the decline in shivering EMG activity.

A similar approach was used in a more recent study claiming to demonstrate the development of non-shivering thermogenesis as a result of cold acclimatization during winter (Nishimura et al., 2012). These investigators measured metabolic rate using indirect calorimetry, and shivering by EMG activity of the pectoralis major in 17 young men during 80-min cold chamber exposures (16 °C) performed once in the summer again during the following winter. The authors reported that metabolic rate averaged about 0.15 kcal/min higher during the cold exposures performed during the winter compared to those performed during summer, but EMG activity of the pectoralis major was the same in both exposures, leading them to conclude that a non-shivering thermogenic response to cold had developed as a result of chronic cold exposure during winter. However, the difference in metabolic heat production between winter and summer was quite small, equivalent to about 30 ml/min of oxygen consumption, which is very close to the limit of resolution for human metabolic rate measured using indirect calorimetry with most metabolic carts. Further, as mentioned above, assuming that EMG activity of a single muscle group

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adequately quantifies whole-body shivering activity is a faulty assumption, since many other muscle groups can be recruited during shivering.

In another recent study (van der Lans et al., 2013), a cold chamber acclimatization program (10 consecutive days, 6 h/day, 15 °C air) reportedly increased non-shivering thermogenesis in brown fat stores of 17 healthy, unacclimatized young men and women. During a standardized 50-min exposure to mild cold conditions in a water-perfused cooling suit before acclimatization, metabolic heat production (measured using indirect calorimetry) of the subjects increased from 1.123 kcal/min in thermoneutral conditions to 1.266 kcal/min, and the authors calculated that about 11% of the 0.143 kcal/min increment (i.e. about 0.016 kcal/min) in metabolic heat production during body cooling was attributable to non-shivering thermogenesis (measured by cold-induced uptake of tracer labeled glucose by the subjects' brown adipose tissue). After acclimatization, metabolic heat production increased from 1.123 kcal/min during thermoneutral conditions to 1.314 kcal/min during cooling, and the non-shivering component was calculated to account for about 18% of the 0.191 kcal/min increment (i.e. about 0.021 kcal/min) in metabolic heat production during cooling. The authors contended that this cold-acclimation enhancement of non-shivering thermogenesis was important from the standpoint of whole-body energy balance, and they suggested that intermittently reducing indoor temperatures to induce human cold acclimatization could be an effective strategy for body weight management and obesity prevention. However, their data indicate that even if cold-induced non-shivering thermogenesis were sustained for 24 h per day, it would only generate an additional 30 kcal/day of metabolic heat production, and whether such an increment in metabolic rate would have implications for body weight loss is debatable.

Regardless, even if the cold-induced increments in metabolic heat production that Nishimura et al. (2012) and van der Lans et al. (2013) observed associated with cold acclimatization are attributable to non-shivering thermogenesis, the magnitude of this non-shivering thermogenesis is probably inconsequential for thermoregulation. Metabolic rate typically reaches 3–5 kcal/min during cold-induced shivering (Sawka et al., 2012), and in one study, shivering was observed to elevate metabolic rate to about 11 kcal/min (Golden et al., 1979). Therefore, on whole, there is currently little evidence that cold acclimatization produces sufficient enhancement of the thermogenic response to cold (shivering or non-shivering) to provide any meaningful thermoregulatory benefit for cold-exposed humans.

The third major pattern of human cold acclimatization, referred to as insulative acclimatization, is characterized by enhanced heat conservation mechanisms (Young, 1996). With insulative acclimatization, thermal conductance at the skin is lower during cold exposure than observed in the unacclimatized state. Typically but not always, with this pattern of acclimatization, cold-exposure elicits a more rapid and more pronounced cutaneous vasoconstrictor response. As a result, the decline in skin temperature during cold exposure is greater in the acclimatized than unacclimatized state.

Evidence for this pattern of acclimatization was first observed in older studies in which thermoregulatory responses of Aborigines living in the central Australian desert were measured while they slept naked outdoors in 5 °C cold air, and compared to responses of unacclimatized European control subjects exposed to similar conditions. At the time when these studies were completed, the central Australian Aborigines were nomadic people who lived out of doors, wore no clothing, and at night they slept on bare ground with little or no protection from the cold. Whereas the metabolic rate of unadapted European subjects sleeping in the cold increased, the Aborigine's metabolic rate remained unchanged as ambient temperature fell, and their deep body core and skin temperatures fell more than in the Europeans, thus thermal conductance (metabolic heat production divided by the core to skin temperature gradient) was less in the Aborigine than unacclimatized Europeans (Hammel et al., 1959; Hicks, 1964; Scholander et al., 1958; Stanton Hicks and O'Connor, 1938). A lower thermal conductance could reflect greater insulation in the body's peripheral shell due to a more pronounced cutaneous vasoconstrictor response to cold as a result of cold acclimatization, or it might simply reflect the lower metabolic heat production (i.e., habituated shivering) in the acclimatized Aborigines compared to unacclimatized control subjects.

More definitive evidence for development of an insulative pattern of cold acclimatization was observed in studies of the Ama diving women of Korea, whose chronic cold exposure experiences were described in the previous section of this paper. Hong (1973) measured maximal tissue insulation (the reciprocal of thermal conductance) of divers and non-diving Koreans from the same community while they were immersed in water cool enough to elicit maximal vasoconstriction, but without shivering. Maximal tissue insulation is a measure of the individual's ability to resist body heat loss during cold exposure. Even after accounting for variations in subcutaneous fat thickness (which also influences maximal tissue insulation as described earlier in this article), the Ama divers exhibited greater insulation than non-divers. Interestingly, the enhanced insulation of the diving women did not appear to be the result of a more pronounced vasoconstrictor response to cold. Hong et al. (1969) measured forearm blood flow and forearm heat loss of diving and non-diving Koreans during immersion in three, progressively cooler water temperatures. Forearm blood flow decreased in both divers and non-divers as water temperature declined, but as shown in Fig. 7, the diving women actually maintained higher forearm blood flow than non-divers at each water temperature. Even more notable, in each of the water temperature conditions, forearm heat loss was less in divers than non-divers, despite the higher blood flow. Thus, this pattern of acclimatization enabled the divers to resist heat loss, while better maintaining blood flow to metabolically active tissue during their work in the water. Hong et al. (1969) speculated that the insulative acclimatization exhibited by the Ama divers represented development of an improved counter-current heat exchange mechanism in the peripheral circulatory system. However, studies to confirm that speculation are not available. Since 1977, the Ama divers have worked

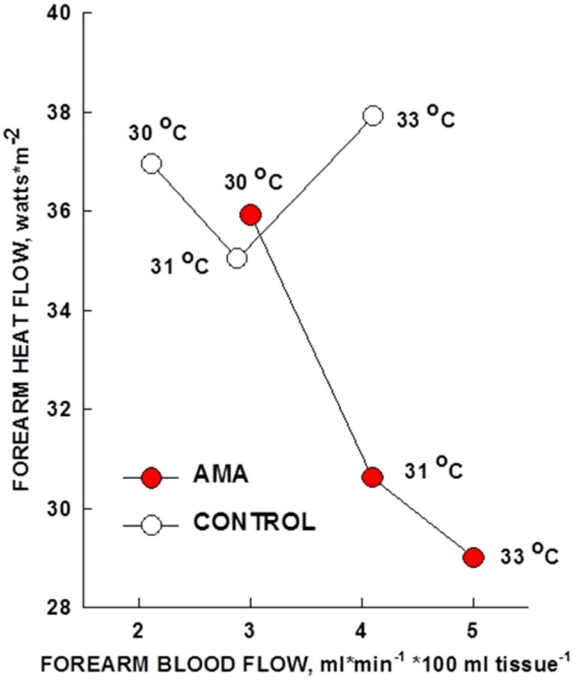

Fig. 7. Forearm blood flow and forearm heat flow during 3 cold water exposures (30, 31, 33 °C) in Ama divers and controls. Forearm blood flow decreased in both divers and non-divers as water temperature declined, but the Ama maintained higher forearm blood flow than non-divers at each water temperature, suggesting a blunted vasoconstrictor response, without the accompanying increase in heat loss. Data redrawn from Hong et al. (Hong et al., 1969)

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wearing wet suits, lessening the cold stress experienced during the diving periods, and in more recent studies of the Ama divers, the insulative pattern of cold acclimatization was no longer apparent (Park et al., 1983).

Studies in which unacclimatized people undergo brief immersions in mild to moderately cold water repeated for a few days or a week, demonstrate that those cold exposure conditions can produce habituation, but are not severe enough to cause the insulative pattern of acclimatization to develop (Lapp and Gee, 1967; Radomski and Boutelier, 1982). On the other hand, longer acclimatization periods employing more prolonged and colder water immersions may produce insulative acclimatization. In a study reported by Young et al. (1986, 1987), healthy young men lacking significant prior cold exposures completed a cold acclimatization program consisting of 90 min of immersion in 18 °C water, repeated five days per week for eight weeks, and developed some physiological adjustments consistent with hypothermic habituation (i.e., blunted thermogenic response to cold), but other adjustments were more consistent with the development of an insulative type of cold acclimatization. For example, following repeated cold-water immersion, cold-air exposure caused a more pronounced rise in blood norepinephrine concentrations and a greater decline in skin temperature than before acclimatization, suggesting that a more pronounced cutaneous vasoconstrictor response to cold had developed. In addition, a smaller increment in blood pressure during cold exposure was observed after acclimatization, while cardiac output responses to cold were unaffected (Muza et al., 1988). The blunting of the systemic pressure response to cold despite pronounced cutaneous vasoconstriction indicated that subcutaneous vascular beds were better perfused following acclimatization. Subsequent studies of the effects of prolonged, daily cold water immersions repeated over several weeks provide similar findings confirming the development of enhanced vasoconstrictor responses to cold under these severe exposure conditions (Bittel, 1987; Jansky et al., 1996a, 1996b; Skreslet and Aarefjord, 1968). An insulative adaptation has also been observed in cold-water swimmers. Golden et al (Golden et al., 1980) showed that swimmers who regularly trained in cold water were better able to maintain core temperature, apparently from an enhanced vasoconstrictor response. More recently, insulative adaptations have also been demonstrated in adult and young children who regularly swim in cold water (Bird et al., 2012; Hingley et al., 2011). Interestingly, during sedentary immersion in cold-water, acclimatized swimmers respond with a decline in core temperature (Hingley et al., 2011), whereas during exercise on cold-water, no decline in core temperature is observed along with a concomitant increase in vasoconstrictor tone. Thus, as was suggested to have occurred in the Korean diving women, acclimatization by prolonged cold-water immersion, repeated over long periods may cause development of mechanisms enabling better heat conservation by improved insulation at the body surface, while perfusion of the subcutaneous shell is more optimally maintained than before acclimatization.

Several studies have examined the role of reductions in skin and/or core temperature in inducing physiological adaptations. O'Brien et al. (2000) had two groups of subjects immersed in cold water (20 °C; 5 $d \cdot wk^{-1}$; 60 $min \cdot d^{-1}$); one group exercised so they experienced a fall in skin temperature but not core, whereas the other group rested during immersion and experienced a decline in both skin and core temperature. A standardized cold-air test was used before and after acclimation to determine physiological changes. Their data show that lowering skin temperature alone (exercise group) caused an insulative or enhanced vasoconstrictor response, but to effect a change in sympathetic nervous activity, both core and skin temperatures (resting group). More recently, Tipton et al. (2013) used a similar experimental design where one group experienced core and skin cooling (45-min immersion in 12 °C water), whereas the other group only experienced skin cooling (5-min immersion). Their findings demonstrated a habituation of the metabolic response during the initial (cold-shock, first 5-min) and middle stages (from 6-min to a −1.2 °C decrease in core temperature) of immersion in the group that had a reduction in both core and skin temperature, with no changes observed in the skin-cooling-only group. These recent findings are in agreement with an earlier study by Golden and Tipton (1988) that demonstrated resting cold-water exposure elicits a blunting of the metabolic response to cold.

4.3. What Determines Which Pattern of Cold Acclimatization Develops?

A theoretical model, shown in Fig. 8, has been proposed (Young, 1996) to explain how the pattern of physiological adjustments that develop with cold acclimatization is determined by the specific nature of the cold exposure and the associated physiological strain experienced. The model's central premise is that the key determinant for whether habituation, metabolic acclimatization or insulative acclimatization develops is the degree to which cold exposure results in significant body-heat loss (Young, 1996). In this construct, repeated short cold

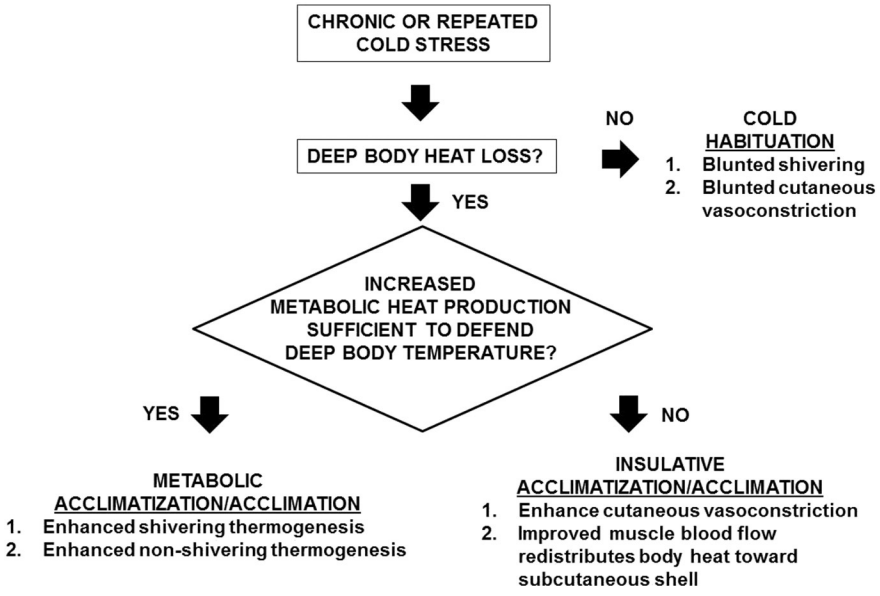

Fig. 8. Flowchart demonstrating a theoretical model of different patterns of human cold acclimatization.

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exposures involving only limited parts of the body and producing trivial whole body heat losses will promote development of habituation. In contrast, repeated cold exposures that are prolonged and/or severe enough to preclude body heat loss being balanced by increased thermogenesis (i.e., deep body temperature declines significantly during exposures) will promote development of insulative thermoregulatory adjustments. The model also incorporates the possibility that the body's thermogenic capability (either shivering or non-shivering) could be improved if repeated exposure to cold conditions produces significant body heat loss, but concomitant increases in thermogenesis are sufficiently to balance body heat loss and prevent significant core temperature declines. Thus, metabolic adjustments would most likely result from chronic exposure to mild or moderate cold environments, whereas insulative adjustments would result from more severe cold exposures. Another possibility, which could be consistent with the model, is that habituation, metabolic acclimatization and insulative acclimatization are not really different types of cold acclimatization, but rather different phases in a progressive development of complete cold acclimatization.

5. Summary

In cold environments, humans maintain thermal balance through behavioral and physiological changes. When behavioral thermoregulatory strategies are inadequate, two primary effector responses are acutely elicited to defend body temperature, cutaneous vasoconstriction and shivering thermogenesis. Cutaneous vasoconstriction decreases heat loss to the environment by reducing the skin-to-environment thermal gradient and is elicited through reflex and local cooling by adrenergic and non-adrenergic mechanisms. Shivering is initiated by decreases in skin temperature, with the intensity affected by the magnitude of changes in core temperature. Maximal shivering increases metabolic heat production ~3–4 times above resting levels. Chronic cold exposure induces three distinct patterns of physiological adjustments: habituation, metabolic adjustments, and insulative adjustments. Habituation causes an attenuated vasoconstrictor and shivering response; a metabolic acclimatization leads to an increase in metabolic heat production, and insulative adjustments cause an enhanced vasoconstrictor response to cold exposure. The type of acclimatization response is dependent on the type and severity of chronic cold exposure.

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