Physiological and molecular mechanisms of cold-induced improvements in glucose homeostasis in humans beyond brown adipose tissue

REVIEW ARTICLE

Clinical Research

Physiological and molecular mechanisms of cold-induced improvements in glucose homeostasis in humans beyond brown adipose tissue

Sten van Beek[1], Dzhansel Hashim[1], Tore Bengtsson[2] and Joris Hoeks[1]✉

Exposure to low ambient temperatures has previously been demonstrated to markedly improve glucose homeostasis in both rodents and humans. Although the brown adipose tissue is key in mediating these beneficial effects in rodents, its contribution appears more limited in humans. Hence, the exact tissues and underlying mechanisms that mediate cold-induced improvements in glucose homeostasis in humans remain to be fully established. In this review, we evaluated the response of the main organs involved in glucose metabolism (i.e. pancreas, liver, (white) adipose tissue, and skeletal muscle) to cold exposure and discuss their potential contribution to cold-induced improvements in glucose homeostasis in humans. We here show that cold exposure has widespread effects on metabolic organs involved in glucose regulation. Nevertheless, cold-induced improvements in glucose homeostasis appear primarily mediated via adaptations within the skeletal muscle and (presumably) white adipose tissue. Since the underlying mechanisms remain elusive, future studies should be aimed at pinpointing the exact physiological and molecular mechanisms involved in humans. Nonetheless, cold exposure holds great promise as a novel, additive lifestyle approach to improve glucose homeostasis in insulin resistant individuals.

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INTRODUCTION

Human physiology dictates that core body temperature is maintained and hypothermia is prevented through peripheral vasoconstriction and the increase in endogenous heat production when exposed to low(er) ambient temperatures. The enhanced heat production can be attributed to the activation of both non-shivering and shivering thermogenic mechanisms, triggered by the activation of the sympathetic (i.e. via catecholamine secretion) [1–3] and somatomotor nervous system [4], respectively. These two processes are well-known to drastically affect energy expenditure and substrate metabolism [5, 6]. Hence, it is not surprising that cold exposure represents a potential novel treatment strategy for obesity-related metabolic perturbations, including insulin resistance and type 2 diabetes mellitus (T2DM). Previous preclinical studies have demonstrated that during cold exposure plasma glucose and insulin concentrations are reduced [7–9], the clearance of plasma glucose is significantly increased [7, 10–13], insulin sensitivity is improved [10, 12], and detrimental metabolic effects of high-fat feeding are reversed [12]. Also in (healthy) humans, acute cold exposure (10 °C for 3 h) significantly increased the clearance of labeled glucose [14] and markedly improved glucose clearance of an intravenous glucose bolus [15]. Since continuous exposure of patients with T2DM to low ambient temperatures is simply unfeasible, these cold-induced metabolic adaptations should persist upon returning to thermoneutrality in order for cold exposure to be considered as a viable therapy. In this context, a study by Iwen et al. [16] demonstrated that insulin sensitivity was improved by ~20% in healthy young males measured after acute cold exposure (~18 °C for 100 min). Prolonged, intermittent mild cold exposure (14-15 °C, 2–6 h/day for 10 consecutive days) also drastically increased insulin sensitivity by ~40% in patients with T2DM, assessed ~16 h following the last cold exposure [17]. A clear understanding of the tissues and underlying mechanisms implicated in mediating these beneficial effects, however, remain elusive to date. Here, we aim to review the current body of literature on the effects of cold-induced improvements in glucose homeostasis in humans and set the stage for future research in this field.

BEYOND BROWN ADIPOSE TISSUE

When it comes to cold exposure, research has primarily focussed on brown adipose tissue (BAT) as a pivotal organ in mediating cold-induced improvements in glucose homeostasis. BAT is an important organ in the maintenance of body temperature during cold exposure, as it dissipates large amounts of heat via

[1]Department of Nutrition and Movement Sciences, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands. [2]Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, Stockholm, Sweden. ✉email: J.hoeks@maastrichtuniversity.nl

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uncoupling protein 1 (UCP1)-mediated uncoupling of mitochondrial oxidative respiration, as expertly reviewed elsewhere [18]. This uncoupled mitochondrial respiration is paralleled by a substantial increase in glucose uptake from the circulation [19, 20], which fostered the belief that BAT could potentially be exploited as a 'metabolic sink' for glucose to improve glucose homeostasis. In line with this hypothesis, stimulation of BAT activity via cold exposure or selective β_3-adrenergic receptor treatment has been associated with significant improvements in glucose homeostasis in rodents [12, 21–23].

However, the contribution of BAT to glucose uptake in humans – especially those with obesity - appears more limited. Evidence shows that BAT mass and activity, as indicated by ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake, are negatively correlated with body mass index and percentage body fat, indicating limited amounts of BAT in individuals with overweight/obesity [24, 25]. Furthermore, prolonged, intermittent cold exposure (14-15 °C, 2–6 h/day for 10 consecutive days) only marginally increased ^{18}F-FDG-positive BAT mass and activity in patients with T2DM, despite a robust improvement in insulin sensitivity of ~40% [17]. Although ^{18}F-FDG uptake may not be equal to BAT thermogenesis, as indicated by unaffected BAT oxidative metabolism and NEFA uptake in individuals with overweight and T2DM during acute cold exposure, glucose uptake in BAT was shown to be lower when compared to healthy controls [26]. Despite a large body of evidence that suggests a substantial role for BAT in cold-induced improvements in glucose homeostasis in rodents, other tissues are likely involved in mediating the beneficial effects in humans.

COLD-INDUCED ADAPTATIONS IN PANCREATIC INSULIN RELEASE

The pancreas is an important regulator of glucose homeostasis due to its ability to tightly control plasma glucose concentrations through secretion of the glucose regulating hormones insulin and glucagon [27]. Stressors that drastically influence plasma glucose concentrations, such as a cold stimulus, also markedly affect pancreatic hormone release. Although it is important to note that plasma glucagon concentrations are increased upon cold exposure [28–32], we here primarily focussed on the effects on pancreatic insulin release due to its relevance in the pathophysiology of T2DM. Thus, several preclinical studies have demonstrated a significant reduction in plasma insulin concentrations at baseline and following a glucose bolus during exposure to low ambient temperatures (2–5 °C) [7, 9, 32–36]. The reduction in basal plasma insulin concentrations during cold exposure has also been reported in humans in some [26, 37], but not all studies [28, 38, 39]. Additionally, a reduced insulin concentration following an intravenous glucose bolus was measured in healthy males during acute cold exposure (10 °C for 3 h) [15]. These (pre)clinical findings combined hint towards a reduced responsiveness of pancreatic β-cells to glucose upon cold exposure, an effect likely mediated via an enhanced sympathetic activity [40, 41].

The effects of cold exposure on pancreatic insulin release do not appear to be long-lasting once the cold stimulus ceases. In rats, the effects of cold exposure (5 °C for 28 or 48 h) on plasma insulin concentrations following a glucose bolus were completely abolished if rats were re-acclimatized to thermoneutrality for 4 [33] or 15–18 h [7] prior to the experiments. Also in humans, acute cold exposure (10 °C for 1 h or 18 °C for 100 min, respectively) [16, 39] or cold acclimation (14–17 °C, 2–6 h/day for 10 consecutive days) [17, 37, 42, 43] did not significantly affect fasting plasma insulin concentrations measured at thermoneutrality after the cold exposure. Moreover, plasma insulin concentrations were either not affected [16] or even significantly increased [39] during an IVGTT or OGTT performed at thermoneutrality directly after cold exposure, respectively. These results suggest that the cold-induced effects on pancreatic insulin secretion are part of a highly integrated system of metabolic adaptations to endure cold exposure, which rapidly normalizes upon returning to thermoneutrality.

THE EFFECT OF COLD EXPOSURE ON HEPATIC INSULIN SENSITIVITY

Following the exposure to a cold stimulus, the liver initiates an array of adaptations to aid in maintaining core body temperature as well as euglycemia, including increasing endogenous heat production and glucose release, respectively. For the purpose of this review, we will focus on the effects of the cold stimulus on glucose handling and insulin sensitivity. To prevent the development of hypoglycemia during cold exposure, the liver undergoes major metabolic adaptations to ensure a constant release of glucose into the circulation. In this regard, several preclinical studies have reported a significant reduction in hepatic glycogen content [31, 44–46], as well as an increased expression and activity of gluconeogenic enzymes [31, 47, 48] upon cold exposure in rats, thereby supporting an increased hepatic glucose production during cold exposure. Also the liver's ability to respond to an insulin stimulus seems to be greatly affected during cold exposure as hepatic insulin sensitivity was markedly improved in male Sprague-Dawley rats on the fifth day of cold exposure (4 °C), as indicated by a significantly reduced hepatic glucose production during a continuous low-dose insulin infusion (0.6 kg/mg/min) [13]. To our knowledge, it remains to be established whether acute cold exposure affects the liver in a similar way in humans. In addition, whether the observed improvements in hepatic insulin sensitivity are conserved upon returning to thermoneutrality is not entirely known and studies about this topic are scarce. Improvements in hepatic insulin sensitivity have been observed in Sprague-Dawley rats following cold exposure (4 °C for 3 weeks), even when rats were reacclimatized to ambient room temperature for 30 min [49]. Prolonged, intermittent mild cold exposure (14-15 °C for 10 consecutive days, 2–6 h/day) in T2DM patients tended to improve hepatic insulin sensitivity ~16 h following the last cold exposure [17], whereas a follow-up study performed at slightly higher ambient temperatures (16-17 °C for 10 consecutive days, 2–6 h/day) did not affect hepatic insulin sensitivity [43].

COLD EXPOSURE AND WHITE ADIPOSE TISSUE GLUCOSE UPTAKE

Upon exposure to low ambient temperatures, the white adipose tissue (WAT) not only plays an important role in the mobilization of free fatty acids (FFAs) to heat producing organs, but also contributes to thermogenesis itself. Despite the fact that WAT is often neglected as an energy consuming tissue, it still accounts for ~6% of the variation in human basal metabolic rate [50] and its energy expenditure can be drastically increased upon cold exposure or β_3-agonist treatment [51, 52]. In line with these findings, prolonged cold exposure (4–10 °C for 48 h – 3 weeks) or norepinephrine infusion (4 days) is associated with an increased glucose uptake into the WAT of rodents in both the basal- and insulin-stimulated state [10, 11, 34, 53, 54] and these effects persisted upon returning to thermoneutrality [11, 55]. Although it can be speculated that the increased glucose uptake is used as fuel for the increased energy demand for lipolysis during cold exposure or restoration of the triacylglyceride (TAG) lipid pool following cold exposure, previous studies have also identified several futile thermogenic cycles occurring in WAT upon exposure to low ambient temperatures. Hence, activation of these futile cycles could potentially be related to improvements in whole-body glucose homeostasis.

White adipose tissue browning and glucose uptake

At thermoneutrality (30 °C), rodent WAT contains relatively large lipid droplets, few mitochondria and is (almost completely)

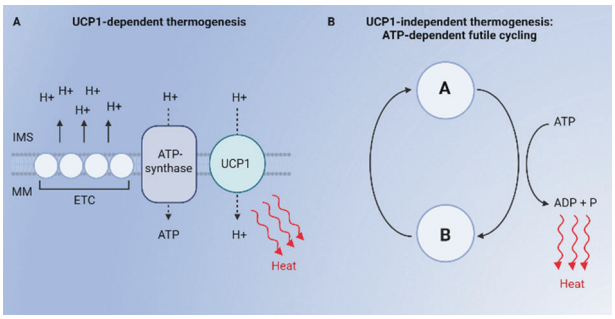

Fig. 1 Schematic representation of uncoupling protein 1 (UCP1)-dependent and independent thermogenic mechanisms. **A** Accumulation of proton (H+) gradient in the mitochondrial intermembrane space (IMS), as a result of the electron transport chain (ETC) function, is the driving force of ATP synthesis via the ATP-synthase complex. UCP1 mediates the leak of protons into the mitochondrial matrix (MM), uncoupling mitochondrial respiration from ATP production and resulting in dissipation of energy as heat. **B** Thermogenic futile cycles are UCP1-independent mechanisms involving two or more interdependent pathways that induce ATP hydrolysis (e.g. re-esterification of glycerol into glycerol-3-phosphate in the TAG/FFA cycle in white adipose tissue, creatine-driven ATP turnover in the creatine cycle and Ca^{2+} transport into sarcoplasmic reticulum in the Ca^{2+} cycle in skeletal muscle) which results in generation of heat. The figure was adapted from a publication by Brownstein at al. [77] and generated using Biorender.com.

deprived of UCP1 expression [54, 56–58]. However, upon cold acclimation [54, 59–62] or prolonged β_3-adrenergic stimulation [59], rodent WAT develops a BAT-like phenotype in a process called WAT browning. More specifically, these brite (brown-in-white) or beige adipocytes develop multilocular lipid droplets, have an increased mitochondrial density, and express UCP1 [56, 59, 62, 63], which is thermogenically functional [60, 61, 64]. Given these BAT-like characteristics, beige adipose tissue has been suggested to function as a 'metabolic sink' for glucose, thereby potentially improving whole-body glucose homeostasis. Indeed, beiging of rodent WAT through cold exposure or β_3-adrenergic stimulation is associated with an enhanced WAT glucose uptake [54, 65] and improvements in whole-body glucose homeostasis [66]. Although the contribution of skeletal muscle glucose uptake to the observed improvement in glucose tolerance was not accounted for in the latter study, skeletal muscle quantity and activity was constant across the experimental groups. Despite these promising results in rodents, evidence for WAT beiging and its putative ability to improve glucose homeostasis in humans is scarce and not unequivocal. Previously, prolonged exposure to mild cold in humans did neither induce WAT beiging markers in subcutaneous WAT biopsies [42] nor improve subcutaneous WAT glucose uptake using PET-CT [17, 37]. On the other hand, exposure of the upper thigh region to cold using an ice-pack for 30 min/day for 10 consecutive days significantly increased subcutaneous UCP1 expression in both lean and – albeit to a lesser extent – individuals with obesity [67]. In addition, subcutaneous WAT biopsies taken from burn victims – who are characterized by markedly elevated concentrations of circulating norepinephrine – showed markers of WAT browning, including an elevated UCP1 expression, citrate synthase activity and mitochondrial respiration [68]. Prolonged treatment (50 mg/day for 12 weeks) of subjects with overweight/obesity with the selective β_3-adrenergic agonist mirabegron also induced markers of WAT browning and improved insulin sensitivity as assessed by means of an euglycemic clamp [69]. Although the authors concluded that these effects were due to WAT beiging and occurred independent of direct skeletal muscle activation, the change in WAT UCP1 expression did not correlate with the improvements in glucose infusion rate whereas the mirabegron treatment did significantly reduce intramyocellular TG levels [69]. Also the possibility that mirabegron directly affected skeletal muscle glucose uptake via β_2-adrenergic receptor activation (see paragraph 6.3) cannot be fully excluded. Taken together, the evidence for functional WAT browning in humans is virtually absent and further studies are required to determine its relevance for humans with respect to whole-body glucose homeostasis.

Futile creatine and TAG/FFA cycling in white adipose tissue

In addition to UCP1-dependent thermogenesis, WAT has also been reported to enhance its energy expenditure through UCP1-independent mechanisms (Fig. 1) [52, 70, 71], such as the futile creatine and TAG/FFA cycle. Similar to UCP1-dependent thermogenesis, activation of these futile cycles enhances energy expenditure and thereby could potentially affect glucose uptake and homeostasis. The futile creatine cycle involves the conversion of creatine into phosphocreatine – and vice versa – in mitochondria to induce an enhanced ATP turnover which is accompanied by the dissipation of heat, as reviewed elsewhere [72, 73]. In line with this, beige adipose tissue of cold exposed mice (1 week at 4 °C) demonstrated an enhanced mitochondrial creatine kinase activity and expression of genes involved in creatine metabolism, suggesting an increased reliance on this futile cycle for thermogenesis during cold exposure [74]. This futile cycle also appears to have marked effects on glucose homeostasis, as adipocyte-specific ablation of key proteins involved in this cycle (such as glycine amidinotransferase or creatine kinase B) is associated with an elevated fasting glucose and a reduced glucose tolerance in rodents [75, 76]. To our knowledge, however, whether this futile cycle is activated in human WAT upon cold exposure, the exact underlying mechanisms of activation and its putative role in the regulation of whole-body glucose homeostasis remain to be established.

Next to the futile creatine cycle, adipose tissue can also generate heat through the futile TAG/FFA cycle independent of UCP1. In short, this can occur via two pathways: (1) FFAs derived from TAG lipolysis are immediately re-esterified in situ into new TAGs (intracellular cycling) or (2) FFAs derived from TAG lipolysis enter the bloodstream and are either stored in hepatocytes or converted into very-low density lipoproteins by the liver, whereafter they are transported back to the WAT (extracellular cycling), as reviewed in more detail elsewhere [72, 77, 78]. Isolated adipocytes from subcutaneous WAT biopsies demonstrated a ~40% re-esterification of FFAs, although a large variation between individuals existed [79]. Furthermore, it was established in white adipocytes isolated from healthy lean donors and donors with obesity that the futile TAG/FFA cycle accounted for ~12% of WAT total energy expenditure and that FFA re-esterification upon isoprenaline showed a negative correlation with BMI [80]. In vivo analyses in healthy young males, using infusion of a stable ^{13}C-palmitate and D-5-glycerol tracer, indicated that ~70% of all FFAs are re-esterified (20% intracellular; 50% extracellular) [81], thereby further demonstrating the thermogenic capacity of the TAG/FFA cycle.

Interestingly, the futile TAG/FFA cycle has been shown to be greatly enhanced upon cold exposure or β_3-adrenergic stimulation in rodent WAT [82, 83]. Similar findings were reported for human WAT, although differences were observed between studies regarding the relative contribution of the intra- and extracellular TAG/FFA cycle. Thus, 3-hours of cold exposure at 5 °C increased the extracellular TAG/FFA cycle, whereas the intracellular cycle remained unaffected [84]. In contrast, both mild cold exposure (18 °C for 180 min) or administration with mirabegron (200 mg) markedly increased the intracellular futile TAG/FFA cycle, with no effects on the extracellular cycling [51]. The latter study further demonstrated the thermogenic capacity of the futile TAG/FFA cycle, as it accounted for ~28% and ~55% of the total increase in energy expenditure upon cold exposure or β_3-adrenergic agonist

administration, respectively [51]. Given the latter, it is tempting to hypothesize that the increase in futile TAG/FFA cycling is inherently associated with an increased glucose uptake. However, it remains to be established whether the TAG/FFA cycle is still fully functional in people with (or at risk for developing) T2DM, and whether it contributes to improving WAT glucose uptake and whole-body glucose homeostasis.

THE ROLE OF SKELETAL MUSCLE IN COLD-INDUCED IMPROVEMENTS IN GLUCOSE HOMEOSTASIS

The skeletal muscle is a metabolic tissue frequently proposed as a pivotal mediator of cold-induced improvements in glucose homeostasis. This is not surprising given the skeletal muscle's extraordinary capacity for substrate oxidation, as well as its prominent regulatory function in maintaining glucose homeostasis [85, 86] which is known to be impaired in T2DM [85]. Several studies have demonstrated robust increases in glucose uptake in a variety of muscles in vivo in both rodents and humans upon cold exposure [8, 10, 11, 17, 19, 34, 49, 87, 88], an effect that appears to occur independent of insulin [34, 88]. This cold-induced skeletal muscle glucose uptake is therefore likely to be an important driving force behind the positive effects of cold-induced improvements in glucose homeostasis. However, the precise physiological processes and molecular pathways mediating these effects are currently unknown and could potentially be attributed to non-shivering thermogenesis, shivering thermogenesis and/or adrenergic stimulation.

Skeletal muscle as a non-shivering thermogenic organ

Before the initiation of shivering thermogenesis, the human body relies on non-shivering thermogenic processes for the production of heat upon cold exposure. As implied by the name, these processes occur independent of muscle contractions and enable the body to maximally increase energy expenditure by ~30% [6]. Although the exact tissues involved in non-shivering thermogenesis in humans is still debated, a substantial role for skeletal muscle has previously been proposed. Upon mild cold exposure (16 °C), individuals with overweight/obesity – typically characterized with lower BAT quantity - demonstrate similar levels of cold-induced thermogenesis as healthy lean individuals [24], suggesting the potential involvement of other tissues than BAT in non-shivering thermogenesis, such as skeletal muscle. In line with these results, cold acclimation of rats (5 °C for several weeks) was shown to significantly increase skeletal muscle glucose uptake independent of shivering thermogenesis [11], hinting towards an increased skeletal muscle energy demand to sustain non-shivering thermogenesis.

The exact impact and origin of skeletal muscle non-shivering thermogenesis is currently unclear, especially in humans. Previous studies have focussed on uncoupling protein 3 (UCP3) – an UCP1 analog expressed in skeletal muscle – and its potential role in mitochondrial uncoupling in skeletal muscle during cold exposure [89–92]. However, the exact role of UCP3 in skeletal muscle non-shivering thermogenesis remains to be further explored, as discussed in more detail elsewhere [93]. In short, several studies have reported an increase in skeletal muscle mitochondrial uncoupling upon acute cold exposure [89–91], albeit that UCP3 protein expression either remained unaffected [90, 92] or tended to increase [89]. Additionally, UCP3 has been associated with an alternative primary function within the skeletal muscle thereby further questioning its role in mitochondrial uncoupling [94, 95].

Apart from UCP3, an emerging body of evidence has suggested a role of futile Ca^{2+} cycling in skeletal muscle non-shivering thermogenesis. Ca^{2+} is involved in various processes, including muscle contraction and intracellular signaling. After its release into the cytosol, it is rapidly transported back into the sarcoplasmic reticulum via the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pump at the expense of ATP [96]. However, the latter process can be regulated via a small molecular weight protein named sarcolipin (SLN), which uncouples SERCA-mediated Ca^{2+} transport, resulting in a futile Ca^{2+} cycle that increases ATP utilization and subsequently heat production [97, 98]. In line with the latter, mice ablated of intrascapular BAT were able to maintain a stable core temperature upon prolonged cold exposure (4 °C for 9 days), independent of shivering, through an upregulation of skeletal muscle SERCA and SLN expression [99]. This effect was abolished entirely in UCP1 and SLN double knock-out mice [100] or iBAT-ablated SLN KO mice [101]. Combined, these results clearly demonstrate a pivotal role of SLN in skeletal muscle non-shivering thermogenesis in rodents, although the underlying pathways through which cold exposure activates this futile cycle are unknown.

It is not surprising that muscle-specific SLN KO or overexpression has been associated with significant decreases or increases in basal energy expenditure, respectively, both in vitro and in vivo [101–104]. SLN overexpression markedly increased whole-body and muscle-specific fatty acid oxidation and transport, as well as mitochondrial density, quality and oxidative capacity [97, 103]. Concomitantly, robust improvements in fasting glucose concentrations, skeletal muscle glucose uptake, glucose tolerance, and insulin sensitivity were observed upon SLN overexpression, whereas SLN KO displayed the opposite phenotype [97, 101, 103, 104]. However, it should be noted that these effects were accompanied by significant changes in body weight and fat mass, thereby limiting robust conclusions of the specific effect of SLN-induced non-shivering thermogenesis on glucose homeostasis [101, 103, 104].

In human skeletal muscle, the expression of SLN is several fold higher as compared to rodents [105], although the role of this protein in human skeletal muscle non-shivering thermogenesis is largely unknown. Hitherto, only SLN protein expression, but not activity, has been measured and compared between metabolically different individuals. In patients with T2DM it was shown that SERCA2 and SLN expression remained unaltered upon prolonged mild cold acclimation [17], and SLN expression was neither significantly different between lean subjects and participants with obesity, nor correlated with body fat percentage or resting metabolic rate [106]. A role for SLN in human skeletal muscle non-shivering thermogenesis thus remains controversial, and should be investigated in more detail.

Shivering thermogenesis and skeletal muscle glucose uptake

Apart from generating physical force, muscle contractions are well-known for the release of substantial amounts of heat – a principle utilized by the body during cold exposure. Involuntary muscle contractions, better known as shivering, occur during cold exposure for the sole purpose of heat production [5]. Shivering is a highly energetic process which is able to maximally increase energy expenditure by ~500% [107]. To sustain this demanding process, shivering thermogenesis is fueled by a combined oxidation of glucose and lipids, as reviewed elsewhere [93]. The majority of the oxidized glucose for shivering thermogenesis is obtained from muscle glycogen stores, which accounts for ~75% of total glucose oxidation [108], whereas the remainder (25%) is taken up directly from the circulation [108]. In line with the latter, shivering of healthy and diabetic rats during acute cold exposure (4-5 °C for 24 or 48 h) markedly increases metabolic clearance of labeled plasma glucose, as well as basal skeletal muscle glucose uptake [8, 10, 11, 19]. Likewise, Vallerand et al. [14] demonstrated that shivering during acute exposure to cold air (10 °C for 3 h) robustly increased clearance of labeled plasma glucose in healthy male volunteers. In fact, shivering intensity was shown to positively correlate with glucose uptake, with a higher shivering intensity being associated with a higher total muscle glucose uptake [87].

Although it is clear that shivering during cold exposure induces skeletal muscle glucose uptake, the underlying molecular pathways remain elusive. In this context, several rodent and human studies have reported shivering-induced skeletal muscle glucose uptake independently from plasma insulin concentrations [7, 8, 26, 87]. In fact, cold exposure has been shown to robustly increase skeletal muscle glucose uptake whilst simultaneously decreasing activation of key proteins of the insulin signaling pathway [34, 88], thereby strongly hinting towards insulin-independent mechanisms. Since shivering can be described as a "quasi-exercising" process during which muscle contractions occur but no external work is performed [109], it may stimulate GLUT4-mediated skeletal muscle glucose uptake through contraction-mediated activation of AMP-activated protein kinase (AMPK) [88].

Adding to the effects seen on skeletal muscle glucose uptake, shivering thermogenesis has also been associated with marked beneficial effects on glucose homeostasis in rodents [7, 8, 10, 11]. In line with these pre-clinical findings, acute exposure of healthy males to shivering thermogenesis (10 °C for 3 h) improved glucose clearance of an intravenous glucose bolus during cold exposure, even though oral glucose tolerance remained unaffected [15]. Upon returning to thermoneutrality, however, shivering thermogenesis appears to affect glucose homeostasis in a time- and/or dose-dependent manner. In this regard, glucose tolerance of healthy males during an oral glucose tolerance test performed 90 minutes after the cold exposure was significantly reduced, potentially due to acute shivering-induced elevation of free-fatty acid concentrations, endogenous glucose production and/or changes in blood flow [39]. With respect to the latter, reduced blood flow to skeletal muscle likely undermines the skeletal muscle glucose uptake during or immediately after cold exposure due to vasoconstriction [110, 111]. Nonetheless, repeated exposure of patients with T2DM to mild cold (14-15 °C, 2–6 h/day, 10 consecutive days) with a certain degree of self-reported shivering robustly improved insulin sensitivity by ~40%, ~16 h following the last cold exposure [17]. Whether or not this effect of cold acclimation is affected by reduced skeletal muscle perfusion during cold exposure is currently unknown.

Altogether, these results suggest that either 1) the beneficial effects of one bout of cold-induced shivering thermogenesis occur after a prolonged period of time upon returning to thermoneutrality or 2) that repeated exposure to shivering thermogenesis is required to achieve beneficial effects on whole-body glucose homeostasis. As such, additional studies investigating the effects of a single-bout of shivering thermogenesis, as well as the effects of repeated exposure to shivering thermogenesis, on whole-body glucose homeostasis are warranted.

Skeletal muscle glucose uptake via β_2-adrenergic receptors

Exposure to cold conditions is well-known for its activation of the sympathetic nervous system (SNS) [1], which has previously been suggested to underlie cold-induced skeletal muscle glucose uptake [11]. Activation of the ventromedial hypothalamus (VMH) via either electrical or chemical stimulation has been shown to significantly increase skeletal muscle glucose uptake in rats, independently of changes in plasma insulin levels [112–114]. Given that cold-induced SNS activity is highly associated with norepinephrine release by sympathetic nerve endings and – to a lesser extent – secretion of epinephrine into the circulation [2, 3, 115–117], skeletal muscle glucose uptake upon VMH stimulation is likely attributed to catecholamine secretion. Indeed, inhibition of postganglionic norepinephrine release via guanethidine treatment during VMH stimulation in rats was shown to abolish skeletal muscle glucose uptake, whereas removing the adrenal medulla – which abolishes epinephrine secretion - did not [114]. These findings therefore indicate that cold-induced skeletal muscle glucose uptake is primarily mediated via local norepinephrine release and is less reliant on circulating epinephrine.

Since norepinephrine binds to adrenergic receptors (ARs) to elicit its metabolic effects, studies have focussed on identifying the ARs involved in skeletal muscle glucose uptake. Although norepinephrine has a higher affinity for β_1- and β_3-ARs [118, 119], the effects on muscle appear primarily mediated via the β_2-AR [120], the major subtype of ARs in myocytes [121]. In vitro evidence shows that selective β_2- and/or β_2-/ β_3-AR agonists promote glucose uptake through GLUT4 translocation [120, 122–126], whereas selective β_1-AR agonists had no effect [120]. Interestingly, incubation of isolated rat soleus or EDL muscle with BRL37344 – a β-agonist specifically designed for the β_3-AR but was recently also shown to bind and activate the β_2-AR – also significantly increased glucose uptake through activation of β_2-ARs [127, 128], hinting towards an in vivo physiological relevance of (β_2-)adrenergic stimulation on skeletal muscle glucose uptake.

However, investigating the in vivo effects of β_2-AR agonists on skeletal muscle glucose uptake is complex. Acute administration of β_2-AR agonists is well-characterized to induce hyperglycemia and hyperinsulinemia [123, 129–131], thereby inherently affecting skeletal muscle glucose uptake. Acute injection with BRL35135 – which was designed as a β_3-AR agonist but was shown to bind to the β_2-AR – has previously been demonstrated to increase skeletal muscle glucose uptake, an effect that was paralleled with increased plasma insulin concentrations [132]. Nevertheless, prolonged treatment (6 days) with the selective β_2-AR agonist clenbuterol markedly increased basal in vivo skeletal muscle glucose uptake independent of changes in plasma insulin concentrations [123], demonstrating an insulin-independent mechanism of in vivo β_2-AR agonist-mediated glucose uptake. In line with these findings – and in contrast to the acute effects [133] – long-term treatment of diet-induced obese (DIO) mice, as well as diabetic rodents, with a selective β_2-AR agonist has been shown to robustly improve glucose tolerance [122, 123, 134–139], significantly reduce plasma insulin concentrations [123, 134, 136, 137] and improve insulin sensitivity [136, 137, 140].

Similar to the effects seen in animals, acute administration of β_2-AR agonists in humans is also highly associated with increases in plasma glucose and insulin levels [141–143]. Acute administration of the selective β_2-AR agonist terbutaline (0.2–0.4 mg) in healthy volunteers significantly increased plasma insulin concentrations as well as leg glucose uptake, although the authors - based on further statistical modeling - concluded the increased glucose clearance to be independent of higher insulin concentrations [141]. Similar to the data in rodents, a marked discrepancy also seems to exist between acute and chronic effects of β_2-AR agonist supplementation in humans. Indeed, 10-day supplementation with the selective β_2-/β_3-AR agonist BRL35135 significantly improves glucose tolerance and insulin sensitivity in subjects with obesity [144]. Although the tissues involved in this process were not identified, the authors found that this effect was entirely due to an increased glucose disposal [144]. To our knowledge, only two studies have previously investigated the effects of prolonged β_2-AR agonist supplementation on skeletal muscle glucose uptake, whereby oral supplementation with the β_2-AR agonist terbutaline sulfate (3 × 5 mg/day for 1 or 2 weeks) significantly increased insulin stimulated glucose disposal by ~29% in healthy young males, an effect that was primarily attributed to an increased non-oxidative glucose disposal of ~45% [145]. Similar beneficial effects have been reported in healthy, young males upon 4-week inhalation with the selective β_2-AR agonist terbutaline (4 mg/day), which enhanced glucose infusion rate during a hyperinsulinemic-euglycemic clamp by ~27% [146], albeit that these effects were paralleled by a significant increase in lean mass. These studies combined demonstrate that prolonged β_2-AR markedly affects skeletal muscle glucose uptake and whole-body glucose homeostasis, although this remains to be established in patients with T2DM.

In addition to the latter, the molecular pathways involved in mediating skeletal muscle glucose uptake upon β_2-AR stimulation

remain mostly elusive. To our knowledge, Sato et al. [122] were the first to investigate these mechanisms, demonstrating that activation of the mammalian target of rapamycin (mTOR) complex 2 (mTORC2) is key for β_2-AR-mediated glucose uptake in both L6 muscle cells and human primary myotubes [122]. These stimulatory effects could be abolished by specific mTOR inhibitors or ablation of the fundamental Rictor subunit of mTORC2 via siRNA [122, 126]. The role of mTORC2 in β_2-AR-mediated skeletal muscle glucose uptake was recently further highlighted in an elegant study by Meister et al. [138], who demonstrated that clenbuterol-mediated improvements in glucose homeostasis are abolished in skeletal muscle-specific Rictor knock-out mice. However, whether mTORC2 is also involved in mediating cold-induced improvements in (human) skeletal muscle glucose uptake remains to be established.

METABOLIC CROSS-TALK

In order to meet the increased energy demands of the body imposed by cold exposure, the metabolic organs discussed above work in tandem by communicating via different signal molecules. This inter-organ communication during and after cold exposure is an important additional factor to consider when assessing effects on systemic glucose homeostasis. The recognized signal molecules potentially involved in this metabolic-cross talk during cold exposure are numerous (as reviewed in refs. [147–149]) and may promote glucose disposal into WAT and skeletal muscle, stimulate thermogenic activity of brown and white adipocytes and improve hepatic metabolite handling [148, 150]. A prominent protein in this context is Fibroblast growth factor-21 (FGF21), which is increased in serum in healthy lean men during cold exposure (2–19 °C) [151, 152]. The increased FGF21 levels upon cold exposure are linked to higher BAT output of FGF21 [153]. In addition, FGF21 has been shown to increase the expression of thermogenic genes in BAT [152] and WAT [154], as well as stimulate WAT lipolysis and glucose uptake into BAT in mice [148]. Under thermoneutral conditions, FGF21 is mainly secreted by the liver and - to a lesser extent - by skeletal muscle, and has been shown to mediate glucose uptake into adipocytes and reduce plasma glucose [155], as well as improve insulin sensitivity [156] in rodents.

Besides FGF-21, also the myokine irisin was shown to be increased by cold exposure and its circulating levels correlated with shivering intensity in healthy male volunteers exposed to 2–19 °C [152]. Furthermore, administration of irisin improved glucose homeostasis by upregulating expression of UCP1 both in vivo in obese mice [157] and in vitro in primary mice and human adipocytes [152, 157, 158]. Thus far, the WAT 'browning' effects of irisin in vivo in humans have mainly been investigated in context of exercise training and failed to show association of plasma irisin/ irisin gene expression with genes involved in WAT 'browning', such as UCP1 [159, 160]. Therefore, further investigations in humans are warranted.

Combined, it seems highly likely that metabolic cross-talk plays an essential role in the effects of cold exposure on glucose homeostasis. Nevertheless, the majority of the supporting evidence is derived from rodent models, and additional human studies are warranted to elucidate the interplay between metabolic organs during cold exposure and its clinical significance for improving glucose homeostasis.

CONCLUSION

The epidemic rise in the prevalence of T2DM, and the concurrent lack of easily adherable and effective treatment strategies for these patients, have highlighted the urgent need for novel therapeutic approaches to improve glucose homeostasis. In this context, cold exposure has presented itself as a highly attractive treatment strategy for T2DM, with several (pre)clinical studies reporting marked beneficial effects on glucose disposal and insulin sensitivity. Observational and epidemiological studies further highlight the therapeutic potential of cold exposure by demonstrating that even mild lifestyle adaptations, such as sleeping and living in colder ambient temperatures are associated with beneficial changes in glucose homeostasis, such as lower postprandial insulin levels and reduced overall insulin resistance in healthy men [161], as well as lower prevalence of T2DM [162] on a population level. More strenuous, practical forms of cold exposure, such as cold water swimming, have also been proven effective in improving peripheral glucose disposal, as indicated by lower plasma glucose levels two hours following glucose ingestion at thermoneutrality [163]. However, such approaches should be utilized with caution by individuals at risk for cardiovascular complications since stronger cold stimuli at lower temperatures have previously resulted in more pronounced changes in systolic and diastolic blood pressure and heart rate, as compared to milder cold stimuli (as reviewed in ref. [164]). It is important to note, however, that these cardiovascular responses were comparable to changes observed during submaximal aerobic exercise [165].

From a mechanistic perspective, the cold-induced improvements in glucose homeostasis are likely primarily attributed to adaptations within the skeletal muscle, albeit that other metabolic organs (such as the liver and WAT) are also expected to be implicated. To date, the (molecular) pathways underlying the latter improvements remain elusive. Nevertheless, a comprehensive understanding of the mechanisms involved could potentially reveal urgently warranted, novel targets for the treatment of T2DM. It is therefore strongly encouraged that future studies within this – relatively unexplored – field focus on a detailed elaboration of the pathways mediating cold-induced improvements in glucose homeostasis in humans. Until that time, turning down the thermostat, taking a cold(er) shower or even removing a sweater could be a safe, sustainable start to improve your metabolic health.

DATA AVAILABILITY

Data sharing not applicable to this article as no datasets were generated or analyzed for the present review.

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ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Joris Hoeks.

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