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Impacts of cold exposure on energy metabolism

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Abstract

Cold stimulation has been shown to regulate glucose, lipid, and amino acid metabolism, while also increasing heat production and energy expenditure in the body. Disordered energy metabolism is a key factor in the onset and progression of chronic metabolic conditiones such as diabetes, obesity, and cardiovascular disease. Recent research has unveiled the myriad pathways through which cold stimulation affects human energy metabolism. This article provides an overview of how cold stimulation affects energy metabolism across the three major metabolic pathways. Furthermore, it explores the implications and potential therapeutic applications of cold stimulation in the prevention and treatment of various metabolic diseases.

Keywords

cold stimulation; energy metabolism; glucose metabolism; lipid metabolism; amino acid metabolism; chronic metabolic diseases

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1 Introduction

Climate change has led to extreme environmental temperatures, which are strongly associated with increased mortality rates. The Global Burden of Disease Study recently identified non-optimal temperatures as one of the leading risk factors for global mortality[1]. Interestingly, low temperatures have been associated with a more pronounced increase in mortality risk compared to high temperatures[2]. Approximately 30 countries worldwide are situated in cold northern regions, cand over half of China's territory qualifies as cold cities, defined by an average temperature below 0°C. Heilongjiang Province stands as a representative region of cold areas in China, where the prevalence of chronic diseases characterized by metabolic disorders is notably high. Addressing the disease burden associated with cold stimulation-related chronic conditions is a critical challenge in current clinical research.

Environmental conditions can significantly impact energy metabolism[3]. Studies indicate that cold stimulation exerts a notable influence on human energy metabolism. The exploration of cold stimulation's effects on energy metabolism aims to uncover the metabolic regulatory mechanisms of the human body in the cold environment. This endeavor seeks novel approaches for preventing or treating metabolic diseases and provides fresh perspectives and directions for clinical application in relevant fields. Thus, this paper provides a comprehensive overview of energy metabolism under cold stimulation, focusing on glucose metabolism, lipid metabolism, amino acid metabolism and metabolic diseases, this paper summarizes the characteristics of energy metabolism, and their implications for metabolic diseases based on recent research findings (Fig.1).

2 Definition of cold stimuli

The definition of cold stimuli varies depending on geographical location. Cold stimulation encompasses any form of stimulation that induces cold sensations in human skin and deep tissues. This includes activities such as cold-water bathing, ice application, cold exposure, and other modalities[4-5]. In animal studies, appropriate temperatures typically range between 22°C and 26°C, with low temperature exposure defined as 4°C[6-8]. For human studies, the optimal temperature is set between 21°C and 24°C, with cold exposure defined as temperatures ranging from 14°C to 19°C or individualized cooling regimens[9-12].

3 Cold stimulation and regulation of glucose metabolism

Under normal conditions, approximately 70% of the energy supply required by the human body is derived from glucose metabolism[13]. Cold stimulation activates thermogenic

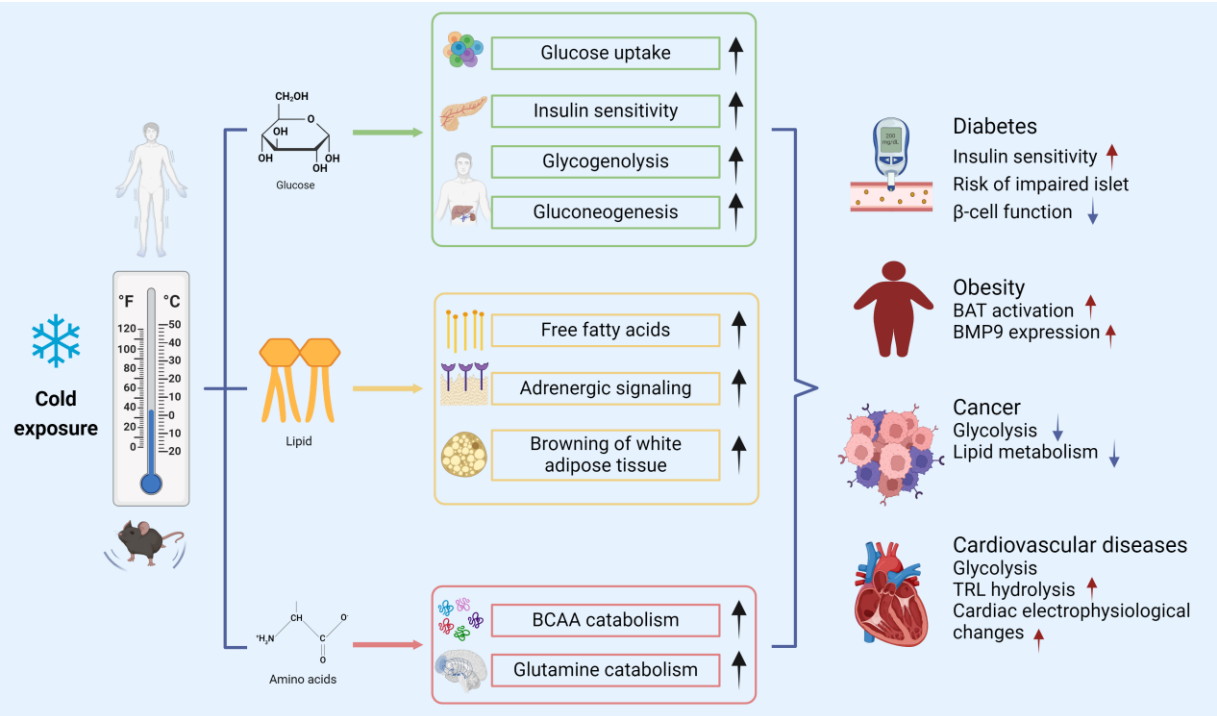

Fig. 1 Cold exposure affects energy metabolism and participates in the occurrence and development of metabolic diseases
BCAA, branched chain amino acids; TRL, triglyceride-rich lipoproteins.

metabolism and promotes glucose uptake by cells. Recent studies employing deuterium metabolic imaging (DMI) have shown a higher labeled glucose signal in rats exposed to cold stimulation (9°C for 1 week), indicating increased sugar uptake[14]. The mammalian target of rapamycin (mTOR), an atypical serine/threonine protein kinase, integrates various extracellular signals such as nutrition, energy, and growth factors[15-16]. Loss of rapamycin complex 2 (mTORC2) impairs glucose uptake in brown adipose tissue (BAT) during cold exposure. However, research by Castro *et al.*[17] suggests that rapamycin complex 1 (mTORC1) activity and BAT glucose uptake were upregulated upon cold stimulation (10 ± 1°C), independent of mTORC2, indicating that mTORC2 deficiency in adipocytes is not necessary for glucose uptake.

Insulin, an anabolic hormone secreted by beta cells, plays a crucial role in carbohydrate metabolism[18-19]. Scheel *et al.*[20] proposed that non-shivering thermogenesis (NST) induced by cold stimulation increases energy expenditure and promotes negative energy balance, potentially improving insulin resistance (IR) in skeletal muscle and adipose tissue. T-box1 (TBX1), a transcription factor involved in mesoderm development, has been found to maintain glucose homeostasis in cold conditions (4°C), and its expression is crucial for proper insulin signaling[21]. These findings suggest the involvement of insulin signaling in glucose metabolism under cold conditions, although the precise mechanism remain to be fully elucidated. Recently evidence suggests that hypothermia exposure enhances whole-body insulin sensitivity[22], potentially mediated by various proteins, adipokines, and mRNAs related to glucose metabolism. Nascimento *et al.*[23] demonstrated that cold-induced increases in peripheral insulin sensitivity involve translocation of glucose transporter 4 (GLUT4). Another study found that cold exposure increased insulin sensitivity through AMP-activated protein kinase (AMPK) or peroxisome proliferator-activated receptor delta (PPAR-delta)-dependent signaling[24]. In addition, cold stimulation (4°C) induces microRNA-485 (miR-485) expression, which promotes the proliferation of BAT progenitor cells, increases BAT mass, enhances NST, and significantly improves insulin sensitivity[25]. Interestingly, Sellers *et al.*[26] confirmed the existence of IR after cold exposure-induced shivering in experiments involving healthy human, providing evidence for the impact of glucose metabolism after cold exposure. These findings suggest that shivering and NST may have distinct effects on insulin signaling in the body under cold stimulation.

Regarding the effects of cold stimulation on glycolysis and gluconeogenesis, it was previously believed that cold stimulation increased the secretion of thyroid hormones,

thereby accelerating energy metabolism, glycogenolysis and gluconeogenesis[27]. However, recent cross-sectional studies by Merchan-Ramirez *et al.*[28] in young healthy adults demonstrated that cold exposure affects thyroid hormone levels independent of glucose metabolism assessed 2 hours after cold exposure. Further investigations into the effects of altered thyroid hormone levels on glucose metabolism during prolonged cold exposure are warranted. Another study showed that cold stimulation (4°C) increased intramuscular conversion of lactate to glycogen (gluconeogenesis) by promoting myofructose-1, 6-bisphosphatase 2 (Fbp2)[29]. The mechanisms underlying these processes remain unclear, and further studies are needed to elucidate the effects of cold stimulation on the different stages of the glucose metabolic pathway.

4 Cold stimulation and regulation of fat metabolism

The human body primarily obtains and absorbs fatty acids through the ingestion and degradation of triglycerides. These fatty acids are then either directly catabolized to provide energy or re-synthesize into triglycerides for transportation to tissues for storage[30-31]. A randomized crossover study has shown that cold exposure (9°C) induces an increase in circulating free fatty acid (FFA) levels in humans, suggesting that cold exposure mobilizes lipids to provide nutrients for thermogenesis in organs[32]. Under periods of energy expenditure, such as cold exposure, triglycerides are released as FFA to support a shift towards catabolism[33]. Pernes *et al.*[34] further observed that triglycerides were the primary lipids affected by cold stimulation, with significant reductions observed at temperatures of 22°C and 5°C. However, studies analyzing serum metabolites in humans have shown a tendency for triglyceride levels to increase during cold exposure[35]. Additionally, Straa *et al.*[4] confirmed through serum lipid profiling that cold exposure gradually increased circulating FFA, peaking at 60 minutes, while total triacylglycerols (TAG) only transiently decreased at 30 minutes. These findings suggest that the effect of cold stimulation on triglyceride is time-dependent and that cold stimulation affects fat catabolism through other pathways.

The mechanisms triggering changes in lipid metabolism induced by cold stimulation are still poorly understood. β3-adrenergic receptors (β3-AR), primarily distributed in adipose tissue, play a crucial role in fat metabolism[36-37]. Zinc-alpha2-glycoprotein (ZAG) is a lipid mobilization factor discovered in recent years that promotes lipolysis[38-39]. Fan *et al.*[40] found that cold stress (6°C) promotes lipid metabolism by increasing β3-AR expression in the ZAG signaling pathway. Moreover, the cold environment can promote triglyceride degradation by stimulating the production of thyroxine (T4), which binds to β3-AR[41]. Hong *et al.*[42] further demonstrated that b-cell translocation gene 2 (BTG2)-deficient mice exhibited reduced fat degradation and lipase expression in response to adrenergic signaling under cold exposure, confirming the essential role of BTG2 in the correct response to β-adrenergic signaling under cold stimulation. These mechanisms are proposed as links between cold stimulation and fat metabolism or as factors that may trigger enhanced fat catabolism.

Cold stimulation promotes lipolysis and metabolism by inducing the browning of white adipose tissue. In mice, this browning process is associated with increased expression of the key thermogenic protein uncoupling protein 1 (UCP1)[43]. The adipokine asprosin reduced the expression of the browning marker UCP1 and other browning-related genes through the transcription factor nuclear factor-E2-related factor 2 (Nrf2), thereby negatively regulating browning and enhancing lipid deposition in adipose tissue[44-45]. Miao *et al.*[44] demonstrated that cold stimulation (4°C) significantly downregulated asprosin expression, thereby promoting the browning of white adipose tissue. In addition, fibroblast growth factor 6/9 (FGF6/9) is a potent inducer of UCP1 expression[46]. A recent study found that FGF6/9 expression is upregulated in response to cold stimulation (5°C), further inducing UCP1 expression[47]. Although potential mechanisms by which cold stimulation affects lipid metabolism through various pathways have been identified, the time dependence of these effects and the specific roles of each mechanism remain to be fully elucidated.

5 Cold stimulation and regulation of amino acid metabolism

Amino acid metabolism plays an important role in maintaining the metabolic balance of the body, involving the conversion of amino acids into sugars, lipids, or the resynthesis of non-essential amino acids. Dysregulation of amino acid metabolism can lead to various related diseases[48-49]. When amino acid metabolism is dysregulated, it will lead to the occurrence of a variety of related diseases[50].

Limited research has been conducted on the effects of cold stimulation on amino acid metabolism. However, recent studies focusing on the metabolism of branched-chain amino acids (BCAAs) and glutamine have garnered attention. BCAAs, including valine, leucine, and isoleucine, serve as signaling molecules regulating various signaling pathways *in vivo*[51]. The dysregulation of BCAA metabolism is implicated in metabolic diseases such as obesity and tumors[52]. Li *et al.*[53] showed through KEGG analysis that cold stimulation (4°C) promotes amino acid catabolism, especially BCAA. Teng *et al.*[54] further found that prolonged cold exposure (7 ± 3°C) promotes BCAA

degradation and inhibits amino acid absorption by inhibiting the expression of amino acid transporters. Similarly, recent findings indicate that cold stimulation mediates BCAA transport by inducing SLC25A44 expression, thereby enhancing BCAA catabolism *in vivo*[55]. These observations suggest that cold stimulation may regulate amino acid metabolism by affecting amino acid transport. In addition, it is found that the knockout of FAM195A, a gene involved in BCAA metabolism, downregulates the expression of multiple enzymes associated with BCAA metabolism, significantly impairing mice tolerance to cold stimulation. This suggests that FAM195A may not only regulate BCAA metabolism but also serve as a potential target for cold stimulation-induced BCAA metabolic disorders[56]. Nonetheless, further studies are needed to identify other factors through which cold stimulation affects BCAA metabolism.

Glutamine (Gln) is an abundant free amino acid in human tissues both intracellularly and extracellularly, with physiological functions including improving immune function, antioxidation, and gastrointestinal nutrition[57-58]. A recently microarray analysis unveiled that cold exposure (10°C) significantly increases glutamine content and the expression of genes related to glutamine metabolism in mice[59]. However, there is still some debates on this issue. Lian *et al.*[60] found, through serum metabolite analysis, that glutamine was downregulated in the 3-day cold stress group (4°C), but no significant change was observed in the 7-day cold stress group, indicating a potential adaptation to cold stress. Further studies are needed to elucidate the specific changes in glutamine metabolism and the underlying mechanisms in response to cold exposure.

6 Cold stimulation and metabolic diseases

In recent years, the prevalence of various metabolic diseases, including diabetes, obesity, and cardiovascular disease, has been steadily increasing, largely due to disorders in energy metabolism[61-63]. Mild cold acclimation has been shown to significantly improve insulin sensitivity in patients with type 2 diabetes. Notably, Remie *et al.*[64] conducted a 10-day mild cold adaptation study (16-17°C) and found that observable overt shivering was necessary to produce the beneficial effects of mild cold adaptation on insulin sensitivity. An epidemiologic study has revealed a direct correlation between elevated environmental temperatures and the risk of gestational diabetes mellitus (GDM) and impaired β-cell function, with a higher prevalence of GDM observed during warmer seasons. Cold-induced BAT thermogenesis may explain this seasonal difference in insulin sensitivity[65].

Obesity is a global epidemic, and cold stimulation is being explored as a potential adjunctive therapeutic strategy to alleviate obesity and associated metabolic disorders by triggering cold-induced thermogenesis. While reduced BAT activation is observed in obese individuals, cold exposure activates BAT in humans, promoting weight loss by modulating metabolic levels[66]. Um *et al.*[67] discovered that cold exposure (4°C) enhances fat metabolism by upregulating the expression of bone morphogenetic protein 9 (BMP9) and activating the thermogenic gene program in adipocytes, suggesting BMP9 as a potential pharmacological intervention for obesity prevention. Interestingly, a study demonstrated that reducing the ambient temperature from 28°C to 20°C resulted in a 125% increase in body weight and subcutaneous fat mass in obese rats, highlighting the significant impact of temperature reduction on promoting weight gain[68]. These findings underscore the need for further investigation into the effects of cold stimulation on obesity, considering specific temperatures and duration of cold exposure.

Most cancers rely on glycolysis for energy generation to fuel their uncontrolled growth, invasion, and metastasis. Cold exposure decreases glucose catabolism systemically and glucose utilization in tumors to inhibit tumor progression[69]. Similarly, Tseng *et al.*[70] found that cold exposure (4°C) decreases circulating glucose levels within tumors, attenuating glycolysis and lipid metabolism, thus impeding tumor growth in mice bearing various solid tumors. . Moreover, Seki *et al.*[71] demonstrated that cold exposure (4°C or 5°C) significantly inhibits the growth of diverse solid tumors, including clinically challenging cancers like pancreatic cancer, suggesting cold exposure as a potential universal approach for cancer treatment. However, some studies have reported increased tumor growth rates in mice implanted with 4T1 triple-negative breast cancer (TNBC) cells following mild cold stress, indicating diverse effects of cold stimulation on different cancer types[72].

Cold stimulation can indeed have both beneficial and detrimental effects on lipid metabolism and cardiovascular health. On one hand, it can ameliorate hyperlipidemia and prevent atherosclerosis by enhancing the hydrolysis of triglyceride-rich lipoproteins (TRL) and accelerating the production of high-density lipoprotein (HDL)[73]. However, there are complexities to consider. For example, exposure of apolipoprotein E (ApoE) and low-density lipoprotein receptor (LDLR) deficient mice to cold exacerbates atherosclerosis, indicating that the effects of cold exposure on lipid metabolism and cardiovascular health are multifaceted[74]. Furthermore, while cold exposure may promote lipoprotein clearance and improve hyperlipidemia, it can also lead to various cardiovascular damages, including alterations in cardiac electrophysiological properties and regulation of ionic currents by AMPK[75-77]. As such, further research is needed to thoroughly understand the mechanisms underlying cold stress-related cardiovascular diseases and to identify potential therapeutic strategies.

7 Summary

Research on the impacts of cold stimulation on energy metabolism has thus far been rather limited and controversial in certain specific areas. These issues may be attributed at least partially to the present lack of established definition and standardized methodologies relevant to the research field. For example, the impacts of cold exposure on human metabolism are likely dependent on the exposure duration, gender differences, and individual variations, among others. However, these issues remain yet to be elucidated. Despite that many studies have generated evidence in support of cold stimulation as a potential approach for the prevention and treatment of metabolic diseases, large clinical trials, particularly those of randomized studies, are still lacking, leaving the findings from animal model studies skeptical in an effort to extrapolate to humans and whether prolonged cold stimulation exerts negative impacts on human metabolism unresolved. These limitations merit more comprehensive addresses through future studies not only with further in-depth mechanistic explorations but also with more clinically orientated analyses.

Author contributions

Yan M and Wang S J wrote the manuscript. Obtained funding: Fang S H, E M Y and Yu B. Administrative, technical, or material support: Fang S H. Supervision: Yu B. Yan M and Wang S J contributed equally to this work.

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Conflict of interest

Yu B is an Editorial Board Member of Frigid Zone Medicine. The article was subject to the journal's standard procedures, with peer review handled independently of this Member and his research groups.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

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