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Unveiling metabolic flux changes during acute cold exposure

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Controlling energy expenditure during acute cold exposure is a fundamental aspect of metabolic dynamics in organisms. However, prior studies on cold-induced thermogenesis faced limitations, primarily focusing on brown adipose tissue (BAT) and lacking precise *in vivo* flux measurements. This editorial aims to highlight the recent research by Bornstein *et al.* providing a comprehensive and quantitative insight into the intricate alterations in metabolic flux that drive this phenomenon[1].

1 Metabolic impact of cold stress and nutrition

Exposure to cold stress induces remarkable physiological changes across various tissues[2], leading to cold-induced thermogenesis. Bornstein *et al.* investigated systemic metabolic alterations in mice subjected to cold conditions. Through untargeted metabolomic analyses of arterial plasma and six distinct organs, they examined a total of 605 metabolites, revealing significant modifications, particularly elevated concentrations of free fatty acids and polyunsaturated monoacylglycerols. These findings underscore a coordinated and intricate systemic metabolic adaptation to cold exposure in mice, extending its impact beyond canonical thermogenic organs to include non-canonical tissues.

BAT plays a pivotal role in heat generation[3]. Its activation involves boosting metabolic activities like fatty acid oxidation and tricarboxylic acid (TCA) cycle, enhancing heat production to maintain body temperature[4]. Bornstein's research emphasizes the significant role of free fatty acid utilization in BAT during fasting in mice exposed to acute cold stress. Moreover, the discernible augmentation in glucose uptake observed in cold-activated BAT may be attributed to its potential role in replenishing TCA cycle intermediates through pyruvate carboxylation. Conversely, under well-fed conditions, glucose assumes a prominent role as the primary substrate for the TCA cycle in various tissues, including BAT.

This intriguing observation suggests that an organism's metabolic response to cold is significantly influenced by its nutritional status, offering valuable insights into the impact of nutrition on thermoregulation and adaptation to environmental challenges. Furthermore, the noted impact of nutritional status on the metabolic response to cold raises intriguing possibilities for investigating the intersection between diet and thermoregulation. Future research efforts could delve into the nuanced ways in which various dietary patterns, such as high-sugar, high-fat, or high-protein diets, impact the efficiency of thermogenesis. This exploration holds practical significance for individuals confronting environmental challenges or seeking to improve metabolic health.

2 Hepatic gluconeogenesis during acute cold exposure

In the fasted state, hepatic glycogenolysis and gluconeogenesis stand as vital mechanisms for endogenous glucose production[5], aiming to elevate blood glucose levels and supplying ample energy substrates for metabolically active tissues such as BAT. Previous work by Nakagawa *et al.* has already established a significant upregulation of hepatic gluconeogenesis in response to cold temperatures[6]. Bornstein's investigation provides a nuanced and rigorous analysis, both qualitatively and quantitatively, highlighting the substantial impact of gluconeogenesis derived from a variety of precursor sources on glucose supply. This holds true both under basal conditions and in the face of acute cold exposure. Despite

the relatively modest contribution of gluconeogenic flux to overall nutrient flux, the disruption in hepatic glucose production markedly diminishes cold tolerance in fasted mice.

This research not only stresses the indispensable role of hepatic gluconeogenesis in maintaining glucose homeostasis but also reinforces the liver's pivotal position as a metabolic nexus[7]. The liver orchestrates the conversion of non-carbohydrate precursors, such as glycerol, lactic acid, and specific amino acids, into glucose. The study sets a high standard of scientific inquiry, offering valuable insights into the intricate dynamics of hepatic gluconeogenesis and its systemic implications.

3 Branched-chain amino acids and 3hb contributions to thermogenesiss

During acute cold exposure, a noticeable increase in circulating branched-chain amino acids (BCAAs) indicates heightened systemic protein breakdown. While previous studies have underscored the importance of BCAA oxidation in BAT[8] and white adipose tissue (WAT)[9] for non-shivering thermogenesis, Bornstein's study introduces a less consistent quantitative perspective. The results meticulously delineate that there is indeed an increased contribution of BCAAs to the TCA cycle in both BAT and WAT. However, it is noteworthy that the level of BCAA oxidation in BAT is conspicuously low, constituting less than 2% of the TCA cycle metabolism. In WAT, this oxidation is nearly negligible. Furthermore, elevated BCAA flux in skeletal muscle suggests a potential involvement in shivering thermogenesis. These results suggest that BCAAs may contribute to heat production in various tissues through diverse mechanisms, possibly involving the mediation of signaling molecules. In addition, 3-hydroxybutyric acid (3HB) is commonly recognized as a significant alternative fuel source[10]. The research also explores the contribution of this ketone body, with surprising findings that BAT minimally utilizes ketones, emphasizing the need for dynamic tracing studies.

This comprehensive investigation reveals critical alterations in metabolic pathways during acute cold exposure, emphasizing the significance of different nutrient utilizations and hepatic gluconeogenesis. Additionally, the application of 13C-isotope tracer techniques demonstrated in this study provides a robust methodological framework for similar future studies, promising further advancements in our understanding of the metabolic intricacies involved in cold-induced thermogenesis. Nevertheless, it is imperative to acknowledge certain limitations inherent in the study conducted by Bornstein *et al.*[1] Notably, the research was confined to a mouse model, and as such, extrapolating the findings to the intricate metabolic milieu of the human body may yield disparate effects. While the insights derived from murine models are indispensable for elucidating fundamental physiological mechanisms, the translation of these observational findings into human physiology necessitates meticulous consideration of potential variations in metabolic responses attributable to differences in body size, specific organ functionalities, and thermoregulation-related disparities. Thus, the broader applicability of the study's outcomes to human metabolic dynamics warrants further investigation and scrutiny in future research endeavors.

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Author contributions

Tang P P drafted the manuscript. Xu H H revised the manuscript. Zhang Y edited and reviewed the manuscript.

Conflict of interest

Zhang Y 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

Not applicable.

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