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HIGHLIGHT

Amino acid restriction in obesity management: Inducing energy discharge

KEY WORDS

Cysteine restriction;
Obesity management;
Weight loss;
Obesity

Control of obesity has been a challenging task worldwide with increasing global burden of obesity-associated complications. Dietary interventions have emerged as a popular approach in obesity control, encompassing approaches such as carbohydrate restriction, fat restriction, and amino acid restriction. Notably, a recent study published in *Nature* reports that animo acid cysteine restriction can induce a rapid weight loss in cystathionine γ-lyase (CSE)-knockout (KO) mice[1].

Cysteine is a sulfur-containing amino acid that features a thiol (-SH) group structurally, which endows it with unique chemical reactivity, enabling participation in disulfide bond formation and redox-related processes. Cysteine is a non-essential amino acid for humans as it can be endogenously synthesized, primarily *via* the transsulfuration pathway from methionine. Methionine, an essential amino acid, converts to homocysteine and then cysteine through the sequential action of cystathionine β-synthase (CBS) and CSE. As a key enzyme in this pathway, CSE catalyzes cystathionine conversion into cysteine with two bi-products of ammonia and 2-oxobutanoate. Cysteine engages in multiple metabolic pathways: it is an intermediate metabolite in the glutathione (GSH) biosynthesis pathway, which is facilitated by γ-glutamylcysteine synthetase (γ-GCS)[2]; it may be metabolized into taurine for osmoregulation and antioxidant functions; it acts as a precursor in hydrogen sulfide (H_2S) production, a gaseous signaling molecule involved in vasodilation and anti-inflammatory processes; it participates in protein synthesis with disulfide bond formation for protein folding and stability; and it has a critical, although underappreciated, role alongside pantothenic acid (vitamin B5) to pathways involving coenzyme A (CoA) synthesis.

The study demonstrated that in CSE-KO mice, cysteine restriction induced rapid and reversible weight loss (30% reduction within 1 week), surpassing other essential amino acid restrictions[1]. Unlike global calorie restriction, the cysteine restriction effect was partially independent of food intake, as cysteine-deprived mice lost more weight than calorie-matched controls. This suggests cysteine restriction may be a strategy for promotion of fat loss while minimizing muscle wasting, as no significant muscle pathology was observed in the model. Moreover, cysteine restriction generated metabolic benefits beyond weight loss, such as reduction in serum triglycerides and free fatty acids. These changes favor the control of obesity-related comorbidities like Type 2 diabetes or metabolic associated fatty liver disease[3]. Weight loss induced by cysteine restriction was fully reversible upon reintroduction of cysteine, suggesting that short-term dietary interventions could be used to jumpstart weight loss without long-term toxicity.

The study found that cysteine deficiency impairs mitochondrial function by depleting coenzyme A (CoA)[1], in which glucose metabolites could not generate acetyl-CoA to enter the TCA cycle in supply of ATP production by oxidative phosphorylation. This metabolic blockage also halts de novo lipogenesis from the lack of glucose-derived acetyl-CoA, leading to increased urinary discharge of glucose metabolites including pyruvate, citrate, and α-ketoglutarate. This forces the body to rely on lipid stores for energy supply, as evidenced by increased white adipose tissue browning ($UCP1^+$ adipocytes). Such mechanisms enhanced fat metabolism in obese individuals, particularly by promoting the conversion of white fat into metabolically active brown/beige fat. The study further identified that the integrated stress response (ISR) and oxidative stress response (OSR) act as key mediators of cysteine deficiency effects on induction of energy metabolism.

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The restriction elevates GDF15 and FGF21 levels suppressing appetite and contributing to energy expenditure, respectively. Collectively, these data suggest that cysteine deficiency induces rapid weight loss *via* cellular events like ISR, oxidative stress, and CoA depletion.

The relationship of cysteine restriction and weight loss was reported in studies of humans and animals[4,5]. Early findings suggest that cysteine deficiency may mediate the weight loss in models of general amino acid restriction. Dietary protein restriction, methionine restriction, or sulfur amino acid restriction all induce weight loss, which is fully reversed by cysteine supplementation[6,7]. In the mechanism, cysteine deficiency was found to impair CoA synthesis and reduce mitochondrial fatty acid oxidation[8]. Moreover, a recent study reinforced the activity of cysteine deficiency in the control of obesity by induction of thermogenesis[9].

The study did not examine the impact of cysteine restriction on insulin secretion. Insulin secretion by pancreatic β-cells is dependent on mitochondrial ATP production from glucose in response to blood glucose elevation, which is dependent on the availability of acetyl-CoA derived from glucose. The insulin secretion may be impaired in the mouse model due to the lack of CoA leading, which is a potential mechanism for the quick reduction of body fat in the KO mouse model. However, this possibility was not addressed in the study as there is no data on insulin. Notably, urinary excretion of glucose metabolites (pyruvate, citrate, and α-ketoglutarate) was increased in the KO model, which supports the perspective. Nutrition loss in urine is an effective approach for weight loss as shown by SGLT2 inhibitors in the treatment of type 2 diabetes[10].

Cysteine deficiency may regulate insulin secretion through two pathways: the classical pathway and the malonyl-CoA/long-chain CoA (LC-CoA) signaling (Fig. 1). In the classical pathway, acetyl-CoA (AcCoA) drives the tricarboxylic acid (TCA) cycle to generate ATP, which activates ATP-sensitive K^+ channels in pancreatic β-cells. This triggers membrane depolarization and Ca^{2+} influx, promoting insulin exocytosis. In the malonyl-CoA/LC-CoA pathway, malonyl-CoA inhibits carnitine palmitoyltransferase 1 (CPT-1), blocking β-oxidation of LC-CoA. Accumulated LC-CoA directly stimulates insulin secretion by modulating intracellular signaling cascades. However, cysteine deficiency may disrupt both pathways through the lack of CoA. Reduced cysteine availability impairs CoA synthesis, decreasing AcCoA production and limiting TCA cycle flux[11]. Concurrently, diminished CoA availability restricts LC-CoA formation and disrupts malonyl-CoA regulation of CPT-1, impairing LC-CoA accumulation. The combined effects, reduced AcCoA-driven ATP production and blunted LC-CoA-mediated signaling, diminish insulin secretion. Decreased insulin levels then promote lipolysis and attenuate anabolic signaling, contributing to the weight loss observed in cysteine-deprived models. Future research could evaluate insulin dynamics in cysteine-deprived models to clarify whether disrupted insulin homeostasis complements the reported metabolic reprogramming.

In summary, the new study establishes a role of cysteine restriction in the control of obesity through two mechanisms of

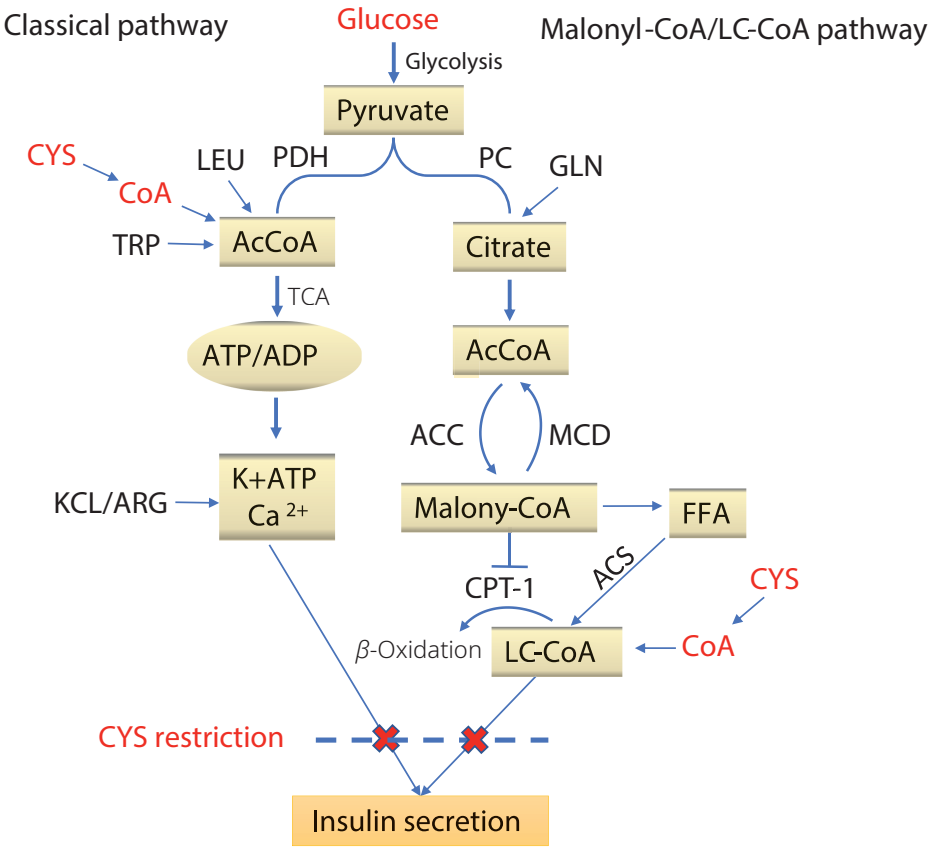

Figure 1 Cysteine restrictions dismiss the insulin secretion by reduced AcCoA-driven ATP production and blunted LC-CoA-mediated signaling.

energy discharge: inducing energy expenditure and promoting energy discharge in urine. These effects can be explained by insulin deficiency. Unfortunately, this possibility was not tested in the study. Additionally, the study focuses on short-term dietary interventions, leaving long-term effects of cysteine restriction on metabolism and health undefined. Prolonged cysteine deficiency could potentially impair glutathione synthesis, immune function, and connective tissue health to cause multiple organ dysfunction. The observations remain to be tested in the human body for safety. Finally, mechanisms linking cysteine deficiency to weight loss remains incomplete even with proposed pathways such as FGF21, CoA, GSH, and others.

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Author contributions

Lili Yu drafted the manuscript. Jianping Ye conceptualized the study and revised the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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