RESEARCH HIGHLIGHT

Fat gain or eat cysteine

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How dietary protein intake regulates physiology and metabolism to influence obesity is not entirely understood. In a recent study published in *Cell Research*, Song et al. found that dietary cysteine contributes to body fat loss by stimulating neuroendocrine hormone signaling.

Obesity and diabetes are global issues posing significant health challenges that need to be addressed. While the mechanisms underlying the metabolic and physiological changes induced by protein intake are not yet fully understood, it has been suggested that a high-protein diet can lead to fat loss.[1] These effects are often attributed to increased energy expenditure and decreased food intake, with endocrine hormones mediating these effects. However, many unknowns remain regarding the molecular mechanisms by which these hormones are regulated by food intake. For instance, as proteins consist of 20 amino acids, it is unclear which amino acids are involved in the observed effects, which cells are affected, and which signaling pathways are activated.

Recent studies have made rapid progress in understanding how dietary protein controls hormone-mediated homeostasis in metabolism, physiology, and feeding behavior. The molecular mechanisms by which dietary protein or amino acids regulate the production and release of various hormones regulating feeding behavior and metabolism are diverse and complex. For instance, in response to amino acid intake in fruit fly *Drosophila melanogaster*, peptide hormones, such as Allatostatin C, diuretic hormone 31 (Dh31), or CNMamide (CNMa), are secreted from the gut, while Female-specific independent of transformer (Fit) or CNMa are secreted from adipose tissue.[2–5] Furthermore, the complex regulation of insulin-like peptides, one of the major amino acid-dependent hormones released from the brain, includes direct amino acid sensing by an amino acid transporter in insulin-producing cells[6] or indirect sensing through other neurons that are regulated by adipose tissue-derived hormones, such as growth-blocking peptides.[7] It has been shown that tyrosine is specifically involved in the production of CNMa hormone from adipose tissue that regulates appetite.[8] However, the specific responsiveness of other peptide hormones to individual amino acids has not been thoroughly tested.

In this issue of *Cell Research*, Song et al.[9] discovered that the amino acid cysteine plays a critical role in fat loss induced by a high-protein diet (Fig. 1). They found that feeding cysteine alone could decrease neutral lipids and suppress food intake, recapitulating the effects of high protein intake in *Drosophila*. From a transcriptome analysis, they found that several genes encoding endocrine hormones, such as short neuropeptide F (sNPF), Dh31, Dh44, and FMRFamide (FMRFa), were induced by cysteine intake. Genetic analysis revealed that fat loss and appetite suppression by cysteine were inhibited when *FMRFa* was knocked out. The tissue(s) in which cysteine is sensed remains unknown, but the authors demonstrated that FMRFa was expressed in some neurons in the subesophageal zone (SEZ) and ventral nerve cord (VNC) and that their neuronal activity was enhanced in response to cysteine. Cysteine intake or genetic activation of FMRFa-positive neurons partially suppressed the shortening of lifespan caused by a high-fat diet. Although cysteine has been reported to specifically influence mechanistic target of rapamycin complex 1 (mTORC1),[10] the current study excludes the involvement of the mTORC1 in FMRFa production. Further research is needed to elucidate the detailed mechanism.

Thus, how does FMRFa function in fat loss? The authors found that the FMRFa receptor (FMRFaR) was expressed in various tissues including the fat body and sugar-responsive taste neurons. In the fat body, cysteine-induced signaling through FMRFaR and downstream protein kinase A (PKA) induced lipid metabolism enzymes, such as lipases, and decreased the neutral lipid content. Moreover, in sugar-sensing gustatory receptor neurons (GRNs), FMRFaR was directly activated by FMRFa-positive neurons, thereby controlling appetite suppression. When FMRFaR expression was specifically knocked down in sugar-sensing GRNs, FMRFa was unable to reduce the sensitivity to sugar, and dietary cysteine failed to suppress food consumption. Previously, it has been shown that dopamine alters the sensitivity of sugar-sensitive GRNs. Starvation increases dopamine release and increases calcium influx into the sugar-sensing GRNs via DopEcR.[11] It would be interesting to examine how dopaminergic and FMRFa-positive neurons, which have opposing effects, are connected to sugar-sensing GRNs.

This study sheds light on the mechanism of fat loss induced by a high-protein diet using *Drosophila* genetics, and the authors confirmed that the mechanism is conseved in mice, with neuropeptide FF (NPFF) acting as the FMRFa ortholog. Their results showed that cysteine supplementation or NPFF administration resulted in anti-obesity effects in mice. While the effects of this mechanism in humans are currently unknown, this discovery opens up new avenues for medical research in developing potential therapies for obesity and related metabolic disorders. Further studies are needed to determine the efficacy and safety of cysteine or cysteine-stimulated hormones in humans.

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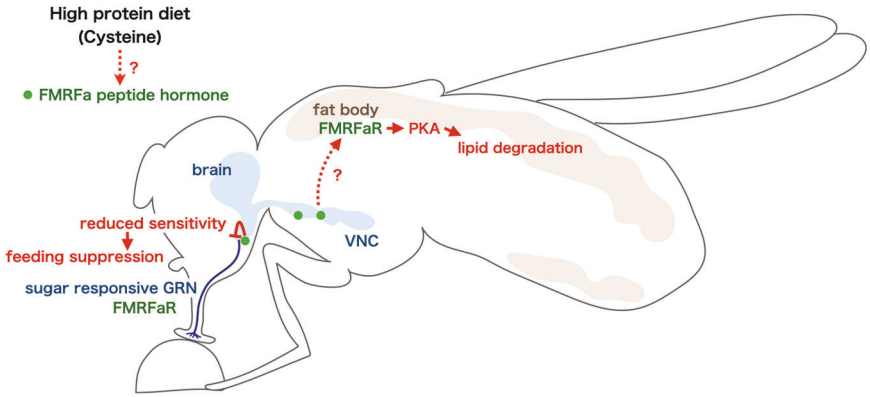

Fig. 1 Dietary cysteine induces fat loss via FMRFa-mediated feeding suppression and lipid metabolism. Upon dietary cysteine intake, FMRFa-positive neurons in the SEZ of the brain and the VNC are activated. In the SEZ, FMRFa-positive neurons appear to inhibit feeding behavior by synapsing with and reducing the sensitivity of several sugar-responsive GRNs that express the FMRFaR. In the fat body, FMRFa triggers lipid degradation by activating FMRFaR and the downstream PKA pathway.

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ADDITIONAL INFORMATION

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