Scholars LITERATURE

Obesity and Diabetes Research

Review Article

DOI: https://doi.org/10.47275/2692-0964-128
Volume 5 Issue 1

Impacts of Essential Protein, Amino Acids in Treating Obesity

Himaja Potla[1*] and Sri Snigdha Gangina[2] and Sushmita Bodagala[3]

[1]Dr. VRK Women's Medical College, Aziznagar, Telangana, India
[2]Rangaraya Medical College, Kakinada, Andhra Pradesh, India
[3]Osh State University, Ak – Bura Campus, Yugo – Vostok 723500, Kyrgyz Republic (Kyrgyzstan)

Abstract

For years, dietary proteins have been used to treat obesity. Losing body fat is beneficial, but losing fat free mass - especially muscle - may be detrimental. Anabolic dietary compounds like proteins might counter fat free mass loss while allowing fat mass loss because protein breakdown predominates over synthesis. When rats are fed a low protein diet, varying the protein quantity decreases muscle anabolic response and increases hyperphagia; but if humans are fed a high protein diet, it promotes lean mass maintenance and satiation. Aside from protein quantity, protein source is also an important metabolic regulator: whey protein and plant-based diets have favorable effects on obesity risk, body composition, metabolic parameters, and fat free mass preservation. It has also been shown that specific amino acids like branched chain amino acids (BCAA), methionine, tryptophan, and its metabolites, and glutamate can positively influence parameters and complications of obesity, especially in rodent models, although there are fewer human studies proving this.

Keywords: Amino acids, Proteins quality and quantity, Obesity, Branched chain amino acids, Methionine, Tryptophan

[*]***Correspondence to*:** Himaja Potla, Dr. VRK Women's Medical College, Aziznagar, Telangana, India.

Citation: Himaja Potla (2024) Impacts of Essential Protein, Amino Acids in Treating Obesity. Obes Diabetes Res, Volume 5.1 DOI: https://doi.org/10.47275/2692-0964-128

Received: March 19, 2024; **Accepted:** May 16, 2024; **Published:** May 20, 2024

Introduction

In both developed and developing countries, obesity has become a major public health problem because it is highly prevalent and has serious complications, such as diabetes mellitus, cardiovascular diseases, respiratory failure, and cancer [1, 2]. An important challenge is finding treatment and/or preventive approaches that target weight loss, its maintenance, and thus the reduction of obesity prevalence.

As a result of obesity, body composition changes reflect changes in fat mass and fat free mass, resulting in altered energy expenditure and food intake and appetite [3]. It is noteworthy that obesity is also associated with various degrees of metabolic impairments, particularly in relation to carbohydrate and lipid metabolism, but it is also worth noting that protein metabolism is also impaired. Muscle quantity and quality are modulated by protein turnover rate, which involves protein synthesis and protein breakdown [4]. Protein metabolism is tightly regulated by hormones, nutrients, and physical exercise on a daily basis. Protein metabolism is strongly regulated after meal intake by amino acids from dietary proteins and insulin secretion. A specific population's protein nutritional requirements are influenced by changes in protein metabolism and whole-body nitrogen balance [5]. In obese subjects, protein metabolism is regulated differently, with a lesser inhibition of proteolysis and a normal or lower response to insulin and amino acids. Obesity is associated with reduced protein synthesis and decreased response to nutrients and exercise at skeletal muscle levels during the fasted state [6, 7]. There is a possibility that these variations in protein metabolism observed in obesity are explained not only by metabolic disorders that accompany obesity, such as insulin resistance or inflammation, but also by changes in body composition during weight fluctuations. For patients with obesity, it is of major importance to consider specific dietary approaches that are based on protein and amino acid intakes in order to lose or maintain weight. These changes affect body composition, energy expenditure, protein intake and appetite, as well as protein metabolism.

Using Proteins to Treat Obesity

Dietary protein quantity and obesity

Overeating and increased energy intake may compensate for unbalanced protein/non-protein intake in a diet and may play a key role in obesity development. The protein leverage hypothesis emerged several years ago. Reduced protein consumption in a diet leads to excess energy intake from non-protein energy nutrients (carbohydrates and fats) to compensate for the energy deficit [8]. Carbohydrates and fats do not exhibit this phenomenon. Roberge et al. found that a lower intake of dietary protein in 8 - 10-year-old children increase the risk of developing a metabolically unhealthy obese phenotype by age 10 - 12 using the QUALITY Canadian prospective study. Dietary macronutrient intakes and obesity phenotypes were studied in a cross-sectional study using Korean National Health and Nutrition Examination Survey data [9, 10]. There was a positive association between low protein intake and metabolically healthy obesity in women. Protein restriction (10% of TEI) to moderate protein restriction (5% of TEI) increases energy expenditure in rats by activating the sympathetic nervous system. The authors also found that rats fed a 10% protein diet were similar to the 5% protein group in terms of lean mass, suggesting that dietary protein intake, but not calorie intake, contributes to lean body mass preservation [11-14]. In animals, protein restriction causes disturbances in calorie intake and energy expenditure. As of yet, there is no clear link between low protein intake and metabolic disorders in obese individuals, nor

does reduce protein intake increase obesity risk. The development of obesity phenotypes is influenced by protein intake, so more prospective studies are needed [15].

High protein intake because dietary protein is known for promoting satiety, energy expenditure through the regulation of meal-induced thermogenesis, and changing body composition in favor of lean mass, it might be interesting to manage obesity using high protein diets [16]. There was no effect with the high protein diet on appetite hormones (GLP1, PYY) or energy intake in obese adolescents, but it did increase meal-induced thermogenesis and fullness scores during meals. Twenty-one severely obese children and adolescents were reduced to 1200 - 1800 calories per day while keeping their normal protein intake. There was limited diet adherence, but patients lost an average of 4.7 kg and family quality of life improved (Figure 1) [17].

Adolescents may benefit from this effect, but younger children may not. At 5.5 and 8 years old, children's plasma metabolomes are similar in the European CHOP study, a double blind, randomized prospective study enrolling healthy newborns fed higher or lower protein formula versus breast-feeding. In addition, high protein formula is more likely to result in obesity at age 6 than low protein formula or breast-feeding during infancy. Fetuses exposed to low or high protein diets during the perinatal period may develop metabolic disorders as adults. An animal study gave a 55% protein diet or a normal protein diet during gestation, a normal diet during weaning, and a normal protein diet or macronutrient choice after weaning [18]. High protein diets during gestation were associated with higher body weight and visceral adiposity, as well as altered insulin liver signaling in pups. Consequently, the beneficial effects of high protein diet interventions during adolescence might be harmful during infancy and pregnancy: however, studies are still needed to verify the exact age at which the effect changes [19].

A higher protein intake is necessary for older obese adults to maintain lean body mass, especially when losing weight or restricting calories. An intervention with high protein amount (1.2 - 1.5 g/kg body weight/day) and 1100 - 1300 kcal per day was administered to 96 overweight or obese adults over 65 years old in a 6-month randomized controlled trial. Based on DEXA measurements, the average weight loss over 6 months was 1.16 kg, 87% of its fat mass loss [20]. A slight increase in mobility and preservation of lean body mass was observed during weight loss. As well as this improvement in fat mass ratio between androids and gynoids, subsequent lipid and glucose plasmatic profiles also improved. Last but not least, maintaining bone density and quality while losing weight was achieved with a hypocaloric, nutritionally complete, high-protein diet. In a recent meta-analysis, also found that very low calorie, high protein diets preserved skeletal muscle mass and decreased fat mass compared to very low calorie, normal protein diets. As a result of diet interventions using high protein intakes in obese older patients, fat can be lost with minimal loss of lean mass, and muscle and bone quality can be preserved [21].

Protein quality impact during obesity

Protein quality - i.e., digestibility and essential amino acid composition - could have differential effects on metabolic or phenotypic changes in obesity, independent of the quantity of protein consumed [22]. The satiating properties of whey protein are higher than those of casein, the other main protein in milk. In older adults, whey protein has been found to be beneficial for preserving lean body mass because it is a 'fast' digestible protein enriched in leucine that stimulates postprandial protein synthesis. A urinary metabolic analysis of Sprague Dawley rats fed a high fat diet (HFD) with 15% protein containing either whey or beef showed lower carnitine, tyrosine, and phenylalanine metabolites, lower creatine/creatinine excretion, and higher tryptophan metabolites: thus, amino acid metabolism may be affected by the protein source [23-25]. The effects of supplementing whey protein on metabolic syndrome among overweight and obese individuals were reviewed in a meta-analysis of 37 randomized controlled trials pooling 2344 participants. Despite heterogeneity in protein doses, body mass index (BMI), age, and follow up duration, whey protein supplementation improved waist circumference, blood pressure, and lipid or sugar plasma levels in this population. In addition to body composition studies, whey protein supplementation and very low-calorie diets and exercise interventions were found to maintain the same fat free mass for obese adults, although there were only 15 participants per group in this study, which had insufficient statistical power. For 8 weeks, Giglio and colleagues [10] randomized 52 obese women to receive either whey protein or hydrolyzed collagen as an afternoon snack. DEXA measurements showed that android fat decreased in the group supplemented with whey, although there was no difference in fat free mass between groups [26] (Figure 2).

Whey protein has also been studied in relation to specific age groups. When a whey protein-enriched drink is used as a preload for lunch, it induces less hunger, more satiety sensations, lower blood sugar levels, and higher anorexigenic hormone secretion than a maltodextrin-enriched drink. Exercise combined with nutrition in sarcopenic obese subjects was analyzed in a meta-analysis of older sarcopenic populations. Combining protein supplementation with exercise did not improve body composition, muscle function, metabolic or inflammatory markers. The study with the highest weight used essential amino acids, but this

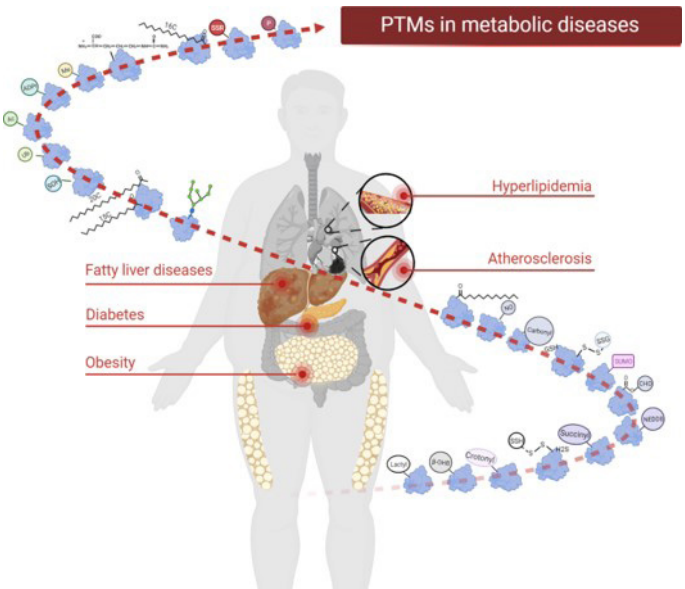

Figure 1: PTM's in metabolic diseases [17].

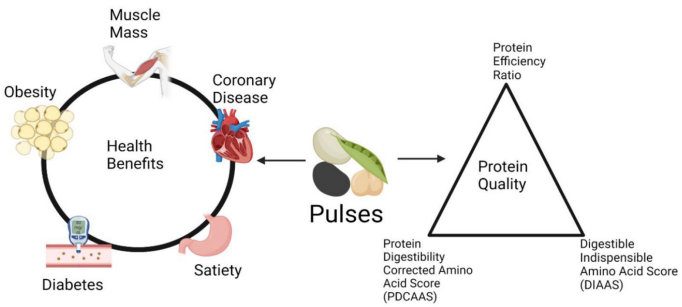

Figure 2: Health benefits of pulses consumption [26].

data came from 153 patients in three randomized controlled trials [27]. Randomized overweight, sarcopenic men to receive either a dairy or non-dairy shake following resistance training for 16 weeks. In all three groups, resistance training significantly increased lean mass measured by DEXA, but dairy shake patients also significantly decreased their fat mass, with an increase in muscle mass to fat mass ratio [28]. There was also a randomized clinical trial in which 26 sarcopenic obese women were given hydrolyzed whey protein or placebo, along with resistance training for 12 weeks. Compared to placebo, the whey group showed a greater, significant increase in appendicular lean soft tissue - which consists of skeletal muscle, skin, connective tissue and tendons - and trunk fat mass, resulting in a decrease in sarcopenia frequency [29].

Randomized controlled trial confirmed whey protein's lipid-lowering properties. The diets of obese and overweight adults were supplemented with whey protein or maltodextrin as well as varying amounts of fiber. Fasting and postprandial lipid profiles improved in the whey protein and low fiber group.

Whey protein supplementation results in a decrease in body fat mass and improvement in metabolic syndrome parameters in obese humans. Additionally, fat free mass is maintained when calorie restriction and exercise are combined [30-34]. Combined with resistance training in older patients, whey protein improves body composition by decreasing sarcopenia, as well as satiety and sugar levels in adolescents.

In contrast to animal protein, plant-derived protein is also an interesting source of protein and is more environmentally friendly than animal protein. Plant sources of protein contain less essential amino-acids such as leucine, isoleucine, valine, lysine, and methionine than animal sources, and plants are less digestible than animals, so they extract less amino-acids for anabolic use [35]. A plant-based diet can actually reduce body weight and body fat, which is interesting for treating obesity, by combining legumes and cereals, for instance. The Food4Me study demonstrates that plant-based diets are beneficial to obese patients. A 6-month intervention of personalized nutrition included online surveys of morphological data, dietary intake, and medical comorbidities from 2413 European adults. Based on a 25 kg/m^2 BMI cut-off, authors found those with the highest BMI consumed the most animal protein and the least vegetable protein; furthermore, substituting 1% of animal protein for vegetable protein reduced overweight and obesity risk [36].

78 participants with varying BMIs, vegans, vegetarians, or non-vegetarians at baseline received an 8-week whole-food plant-based diet group intervention that resulted in a two-point loss of BMI and improved lipid plasmatic profiles as well as mean blood pressure parameters, although the effect was smaller if patients had already been vegan or vegetarian [37]. A randomized controlled trial involving obese and overweight adults fed either a vegan diet or a classical diet over 16 weeks showed that vegans lost 2 points in their BMI, 4.3 kg of fat mass by DEXA, and had a lower insulin resistance index [38]. The decrease in fat mass was correlated with a decrease in animal protein and leucine intake and an increase in plant protein intake, and specific amino acids, such as leucine, were positively correlated with an increase in fat mass, whereas histidine was positively correlated with a decrease in insulin resistance. Based on gastrointestinal hormone secretion and satiety sensations, there may be a mechanism for this. A 60-male adult intervention, consisting of a type II diabetes group, a BMI and age-matched group and a healthy group, found that eating two test burgers containing tofu or meat and cheese at a one-week interval, in random order, increased satiety, postprandial GLP1 levels and amylin levels in tofu eaters [39, 40]. Vegetable proteins may have a weight-reducing effect since GLP1, and amylin are hormones involved in satiety. In a study involving 22 obese patients for 24 weeks, compared lifestyle changes with yogurt enriched with soy as a meal replacement. By replacing meals with soy protein and encouraging lifestyle changes, body weight, intra-liver lipid content, and subcutaneous fat mass improved similarly to baseline. Contrary to the latter group, soy protein reduced waist circumference and triglyceride levels more effectively [41, 42].

A summary of the available evidence indicates that vegetable protein sources may be beneficial to obese individuals' body composition, metabolic parameters, and liver steatosis. This therapeutic intervention should be studied with longer interventions and multiple gastrointestinal hormone and satiety measures before being used.

Bariatric surgery and protein changes

In light of the importance of protein quality and quantity for obesity patients, how do therapeutic interventions like bariatric surgery affect protein digestion and metabolism? Roux-en-Y gastric bypass (RYGB), the gold standard surgery, has restrictive and malabsorptive consequences, as reviewed recently: regarding protein intake, the gastric pouch becomes smaller, so protein intake decreases, and the gastric enzymes necessary to activate pancreatic protein digestion enzymes might be less secreted with RYGB, possibly resulting in a delay between protein ingestion and pancreatic enzyme interaction. Ingestion of protein and pancreatic enzymes might be affected similarly by sleeve gastrectomy, which is more widely practiced because it is only restrictive, not malabsorptive. The optimal daily protein intake increases to 1.5 g of protein/kg of ideal body weight when these changes are taken into account. A validated method such as nitrogen balance was used in a study to determine protein requirements in morbidly obese patients before, 3 and 12 months after surgery [43]. At both 3 and 12 months, the calculated protein requirements are higher than expected. As a result, new recommendations can be made regarding the post-bariatric protein intake. As a result of lower protein intake postoperatively, the risk of sarcopenic obesity increases. Weight loss and fat mass loss are associated with higher protein intake following bariatric surgery. At 3 and 18 months following RYGB or sleeve gastrectomy, two recent prospective studies found a higher protein intake was associated with a higher weight loss. According to a cross-sectional study in 60 women who did not have an operation versus those who did, and who regained weight or not, lower protein intake increased weight regain risk and was correlated with lower satiety feelings after a test meal. Smelt and colleagues found that protein intake significantly affected postoperative handgrip strength, a measure of muscle strength, after RYGB or sleeve gastrectomy. In their 18-week, randomized, controlled study, Obert and colleagues randomly assigned 26 obese women operated by RYGB to three groups: a control group, a group supplemented with whey protein, two powder drinks daily at a dosage of 48 g, and a group supplemented with whey protein 3 times per week. While they did not uncover a significant difference in lean mass loss between groups, the group combining exercise and protein supplementation showed significant improvements in muscle strength in lower and upper limbs relative to body weight and protein intake for patients who completed the whole study [44-46].

The post-operative study comparing RYGB to sleeve gastrectomy at 18-months, or the cross-sectional study mentioned above, did not demonstrate how changes in food tolerance or hunger/satiety affected protein intake. Also examined the impact of bariatric surgery type on macronutrient intake: protein intake decreased postoperatively for all types of surgery, but this decrease was not significantly different. As a result of their 6-month prospective study of 43 patients who underwent sleeve gastrectomy or RYGB, postoperative protein intake decreased in both groups, but protein intake, its share of total energy, and body

composition did not differ significantly between surgery types [47]. In the initial phase after bariatric surgery, protein intake is decreased, but not too much as this can affect the outcome of the surgery. Changes in food preferences, nutritional sensations, and surgery type do not explain this. Additionally, resistance training and protein supplementation may promote muscle growth and prevent the loss of fat-free mass.

Using Specific Amino Acids to Treat Obesity

Amino acid composition, changes in obesity and after therapeutic interventions

What role do individual amino acids play in obesity beyond protein intake? Insulin secretion and insulin resistance are associated with changes in plasma amino acid profiles during obesity. Between 2010 and 2012, 9734 patients aged 20 to 74 using questionnaires. In total, 4118 respondents were included, 3009 of whom were normal weight and 1109 of whom were obese. Lysine, phenylalanine, threonine, histidine, cysteine, tyrosine, proline, serine, and diacid amino acids were inversely associated with obesity risk. Since high fat diets induce higher liver levels of branched amino-acids, alanine, glutamate, and methionine in rodents, while lower levels of glycine and taurine are observed. Several other authors have focused on identifying metabolomics amino acid signatures that differentiate weight regain after RYGB [48]. It was found that weight regain was associated with a decrease in metabolites associated with the serine, glycine, threonine pathways, alanine, phenylalanine, and glutamate metabolism several years after the intervention. In other words, the lower these metabolites, the higher the weight gain.

Through their interaction with the target of rapamycin (mTOR) complex, amino acids play a role in insulin signaling. The mTOR pathway can form two complexes, I (mTORC1) and II (mTORCII), the former integrating amino acid availability to induce protein synthesis. Phosphoinositide-3-kinase (PI3K)/AKT pathways are activated after insulin binds to insulin receptor substrate (IRS). By activating Akt, the TSC complex, an inhibitor of RHEB, moves from the lysosome to the cytoplasm, disinhibiting RHEB from activating mTORC1. Ragulator regulates mTORC1's lysosomal localization by recruiting amino acids in the cytosol to the lysosome via a GTPase, Rag. A transmembrane transporter, SLC38A9, is activated by arginine to transport leucine, isoleucine, methionine, and tryptophan from the lysosome to the cell. A liver protein secreted during fasting, FGF21, also crosstalks with the mTORC1 complex, extending lifespan, improving insulin sensitivity, and diminishing adiposity and liver steatosis. As a result of labeling stable isotopes in cell cultures and stimulating the cells with FGF21, Minard and colleagues mapped the FGF21 signaling network in T3-L1 adipocytes [49-52]. According to phosphorylation analyses, mTORC1 was phosphorylated by FGF21 in these cells as well as in mice injected with FGF21. Mitogen-activated protein kinase (MAPK) mediated this action of FGF21 on mTORC1. In vitro inhibition of mTORC1 with rapamycin impaired FGF21-induced glucose uptake, adiponectin secretion, and uncoupling protein 1 expression in adipocytes. Through crosstalk with FGF21, mTORC1 is a major protein in amino-acid sensing pathways that has beneficial effects on metabolism [53].

BCAAs

BCAAs play an important role in the pathogenesis of metabolic disorders such as obesity and diabetes both in animals and humans. Felig et al. [39] reported the presence of higher circulating BCAA levels in obese individuals for the first time. A recent study found that BCAA plasma concentrations were higher in older subjects with both high body fat and lean mass, suggesting that BCAA levels may also be elevated in older people with obesity but with a specific body composition that increases both fat and lean mass. As BCAA concentrations increased, circulating insulin levels increased, suggesting insulin resistance is the cause of the elevated BCAA concentrations. Several metabolic studies have shown that higher levels of BCAA, phenylalanine, and tyrosine were associated with an up to 5-fold increase in the risk of future type 2 diabetes development. In obese individuals, dietary and behavioral weight loss interventions improved insulin sensitivity [3, 54]. Diabetes was more likely to occur in patients with elevated BCAAs in the Framingham Heart Study. In a recent study, an *in vivo* isotopes study coupled with metabolomics analysis to analyze total BCAA metabolism in db/db mice. Skeletal muscle oxidation is shifted away from white adipose and liver in db/db mice. Fat and liver oxidation are suppressed, which is consistent with reduced expression of enzymes involved in BCAA oxidation (BCATs and BCKDH). Skeletal muscle BCAA oxidation is driven by reduced BCAA oxidation in white fat and liver.

There is also the possibility of dysbiosis in the gut microbiota contributing to the elevation of circulating BCAAs. The positive correlation between microbial functions and IR is largely driven by a few species, notably *Prevotella copri* and *B. copri*, which may directly influence host metabolism. In mice fed a high-fat diet, that a challenge with *P. copri* increased circulating BCAA levels, insulin resistance, and glucose intolerance [55]. As a result of dysbiosis of the human gut microbiota, insulin resistance is associated with the serum metabolome. According to a recent study in overweight and obese adults, gut microbiota metabolites were associated with diabetes-related outcomes independent of changes in BCAAs, indicating other pathways are likely to be involved.

A HFD supplemented with BCAAs also contributes to obesity-associated insulin resistance in rats. Type 2 diabetes risk is positively associated with dietary BCAA intake in human observational studies. Insulin resistance and BCAAs remain controversial. BCAA supplementation has been shown not to impair glucose metabolism in obese, prediabetic patients [56]. In contrast, after four weeks of daily BCAA supplementation (20 g/day), glucose metabolism tended to improve. There was no increase in circulating BCAAs or BCKAs after BCAA supplementation.

Sulfur Based Amino Acids as a Potential Therapy for Obesity

In addition to limiting protein intake moderately, what happens when you restrict amino acids completely? Three weeks of HFD protein-free diets (0% of TEI) were used to induce hypophagia, increase energy expenditure, insulin sensitivity, thermogenic and FGF21 gene expression in muscle and brown adipose tissue, and lower body weight, fat, and lean mass in obese CD rats. Also, these same rats had lower levels of essential amino acids than controls: threonine, tryptophan, valine, phenylalanine, leucine, isoleucine, and lysine, histidine, and methionine [57]. In view of the loss of lean mass involved in a protein free diet, one wonders if restricting specific amino acids like methionine would have the same effect. Plant proteins contain less methionine than animal proteins. It mimics the effects of protein restriction with the exception that food intake increases, and lean mass remains the same. Currently, only one randomized controlled double-blind study dedicated to obese patients allocated 26 adults to a methionine diet for 16 weeks without any significant difference in weight, insulin sensitivity, or fat mass [58].

Since methionine restriction is more easily achievable than protein restriction, it might become a therapeutic approach for obese patients, with the goal of improving body composition, metabolic syndrome components, inflammation, and oxidative stress. On body weight and composition, insulin sensitivity, and sympathetically mediated energy

expenditure, methionine restriction in rodents reproduces the benefits of total amino acid restriction. In diet-induced obesity rodent models, methionine restriction can result in either hyperphagia or transient hypophagia [59-62]. As a result of a crosstalk between adiponectin, an adiponectin-derived factor, and adipose tissue, adiponectin restriction improves glucose metabolism and insulin sensitivity in obese mice. By incubating skeletal muscle cells with adiponectin, glucose uptake is increased, and glycolysis is enhanced. Methionine restriction results in high levels of plasma adiponectin in mice that have been induced to become obese by diet. In male C57BL/6 J mice fed a 10 weeklong HFD to induce obesity, restricting methionine increases plasmatic as well as skeletal muscle adiponectin, inhibits the mTOR pathway, and increases MAPK and IRS-1 mRNA levels in gastrocnemius muscle, improving insulin sensitivity [63].

As a result of methionine restriction, lipid profiles and hepatosteatosis are also improved in DIO mice models. During a 21-week HFD, methionine restriction reduced lipogenesis/lipid catabolism, improving lipid accumulation and liver function. Among the widely used models for studying "lean NASH" is a methionine and choline deficient diet in mice without DIO. In C57BL/6j mice fed a 22-week HFD, methionine restriction also improved liver protein metabolism by increasing retention efficiency compared to controls with obesity but not methionine restriction [64-66]. As a result of methionine restriction, liver protein degradation is upregulated, and protein synthesis is downregulated in this study.

DIO increases pro-inflammatory cytokines and lowers anti-inflammatory levels, as well as negatively affecting the pro-oxidant/antioxidant stress balance in favor of oxidative stress. When C57BL/6 J mice were fed a 10-week HFD, restricting methionine reduced pro-inflammatory cytokine levels and increased anti-inflammatory cytokine levels in the plasma and hippocampus. Furthermore, methionine restriction increases plasmatic levels of hydrogen sulfide (H_2S) by upregulating methionine transsulfuration pathways. Homocysteine is converted to cysteine after methionine catabolism [67-71]. When further degrading homocysteine or cysteine, H_2S is produced as a byproduct. H_2S is a known liver metabolite that enhances lipid metabolism, increases glucose production, and decreases oxidative stress. A positive correlation was found between H_2S production and protein anabolism, while a negative correlation was found between H_2S production and protein catabolism. Thus, mice with DIO with methionine restriction have improved liver metabolism and inflammation by alleviating oxidative stress through endogenous H_2S production [72-75].

During acute exercise, plasma methionine concentrations decrease while transsulphuration metabolites and glutathione biosynthesis metabolites increase. A study in humans examined plasma metabolite concentrations, including those containing sulfur, following acute and long-term exercise. We recruited 26 sedentary middle-aged men with a BMI below 27 kg/m^2 or dysglycemic men with a BMI between 27 and 32 kg/m^2 and impaired fasting plasma glucose, glucose tolerance or insulin resistance [76]. During a 12-week period, the authors alternated two acute challenges on bicycles with high intensity resistance and endurance exercises. Plasma metabolite concentrations changed significantly after long-term exercise due to glutathione biosynthesis and transsulphuration. The strongest correlation rate was found with total plasmatic cysteine, which correlated with changes in insulin sensitivity. The results suggest that exercise can improve insulin resistance in overweight patients by decreasing methionine and metabolites alongside diet [3, 77-79].

As shown in rodent models of diet-induced obesity and a human study reviewed here, methionine restriction has positive effects on health. Further, moderately reducing protein but keeping methionine levels the same does not normalize metabolic responses in DIO rat models. An additional sulfur amino acid, cysteine, can reverse the effects seen above in mouse models regarding energy expenditure, weight gain, lipid levels, insulin levels, and adiponectin levels. The effect of methionine restriction is bypassed by cysteine, since it is downhill of the methionine signaling pathway. The glutathione biosynthesis pathway adapts to low cysteine and methionine diets in normal weight humans: methionine plasmatic and urinary metabolites are low, but total cysteine remains unchanged, suggesting compensatory mechanisms are used to counter low amino acid availability [80-83]. In order to validate this data and optimize therapeutic interventions, future studies are needed restricting all sulfur-containing amino acids in rodents and humans [84].

Other Amino Acids

According to a recent review, tryptophan restriction in a diet promotes longevity in mammals. During moderate restriction, tryptophan increases thermogenesis and food intake, whereas during severe restriction, it decreases energy expenditure, food intake, body weight, fat, and lean mass. Compared to the control diet, fed C57BL/6 J non obese mice the same amount of protein with varying proportions of BCAAs [85]. A higher proportion of BCAAs and a higher food intake were associated with obesity in the groups with the highest proportions of BCAAs. It is interesting to note that tryptophan, threonine, and methionine levels were stable across groups, and that an increase in BCAA, either by tryptophan or threonine, was able to reverse hyperphagia to a normal level. Consequently, a high BCAA diet results in an amino-acid imbalance, resulting in secondary hyperphagia: this phenomenon rather than BCAAs' toxic effects leads to subsequent obesity, hepatosteatosis, and premature aging [3, 86].

In addition to tryptophan itself, its metabolites (endogenous such as serotonin or derived from gut bacteria) disturb metabolism and appetite in obese individuals. An intestinal serotonin blocker decreased serum and intestine levels of serotonin in male C57BL/6 DIO mice. Compared to controls, weight gain slowed, and blood glucose and lipid values improved. Antibiotic treatment reduced plasmatic indole-3-propionic acid, a tryptophan gut bacteria derivative, and increased weight gain in rats fed a standard diet. C57BL/6 mice fed a high fat, tryptophan-free diet lowered levels of indole, another tryptophan metabolite whose plasma levels are low in obese adolescents when colonized with microbiota from control mice. As a final point, tryptophan restriction effects vary with age and only partially simulate total amino acid restriction. Tryptophan restriction affected body composition and hepatic protein sensing differently in 6-week-old male DIO rats compared with total amino acid restriction [87].

In summary, directly or indirectly restricting tryptophan through other amino acid imbalance impacts both endogenous metabolites and bacterial-derived metabolites in contradictory ways. As compared with a control diet, inducing a tryptophan-rich diet decreased body weight, food intake, tryptophan metabolite concentrations and impacted behavioral tests in non-obese adult rats. The restriction of histidine, another aromatic amino acid, also affects food intake, body weight and composition, as well as the synthesis of liver protein. In order to take into account age-specific effects, further research on total aromatic amino acid restriction should be planned similarly to BCAA research.

There is debate over the role of glutamate in obesity as another potential treatment. A food additive known as sodium salt of glutamic acid, induced oxidative stress, inflammation, glucose intolerance, and NAFLD in rats when administered at 2 mg/kg of body weight. There

was little replication of these results in humans, probably because this amount is not physiological. This review focuses on glutamate's role in regulating appetite and adiposity in obesity and its neuromodulatory properties [88].

Appetite is modulated by glutamatergic signaling. In transgenic mice developed to reveal glutamatergic receptors in neurons by fluorescence, leptin injection after food withholding reveals glutamatergic signaling neurons. In electrophysiological experiments on mice brain slices, orexigenic neuromodulators inhibit and anorexigenic neuromodulators stimulate these neurons. A final mechanism for inhibiting food intake by glutamatergic signaling appears to be through anorectic POMC neurons being stimulated. Despite this, metabolite analyses showed that plasmatic and hippocampal glutamine levels increased with 60% HFD in DIO male C57BL/6 J fed 10%, 45% or 60% fat for 6 months without changes in glutamate levels. Through glutamine and hypothalamic glutamatergic neurons, glutamate as a metabolite might influence appetite regulation [89].

As well as serving as a neurotransmitter, glutamate also plays a role in adiposity and body weight. 65 healthy lactating women were tracked prospectively along with their children's body weight for the content of free amino acids in their milk. The glutamate concentration was higher in the fast weight gain group than in the slow weight gain group. The administration of glutamate to a standard diet decreased body fat weight and increased short chain fatty acid levels in adult pigs. Researchers studied food preferences and anthropometrics of 1839 randomly selected children in a subsample of a multicentric European cohort investigating childhood obesity risk factors. Umami flavor preferences induced by 1% monosodium glutamate added to high fat crackers were associated with lower BMI z-scores, lower arm circumferences, and lower fat mass. A biomarker for visceral adipose tissue has been identified in 59 healthy women with BMIs between 20 and 41.1 kg/m^2. It can be used to regulate appetites, improve cognitive performance, manage body weight and adiposity, and measure visceral fat in humans at physiological doses.

Conclusion

Therefore, varying proteins, both in quality and quantity, can be considered a treatment for obese patients' body composition, metabolic syndrome parameters, and appetite regulation. By combining protein supplementation and exercise, therapeutic interventions like bariatric surgery can avoid unfavorable effects on protein intake. Lastly, specific amino-acid restrictions such as BCAA, methionine, tryptophan, and glutamate might be better therapeutic interventions than protein modulation in general, with more human studies needed for validation.

Acknowledgements

None.

Conflict of Interest

None..

References

1. Guillet C, Masgrau A, Boirie Y (2011) Is protein metabolism changed with obesity? Curr Opin Clin Nutr Metab Care 14: 89-92. https://doi.org/10.1097/mco.0b013e328341389e
2. Moon J, Koh G (2020) Clinical evidence and mechanisms of high-protein diet-induced weight loss. J Obes Metab Syndr 29: 166-173. https://doi.org/10.7570/jomes20028
3. Simonson M, Boirie Y, Guillet C (2020) Protein, amino acids and obesity treatment. Rev Endocr Metab Disord 21: 341-353. https://doi.org/10.1007/s11154-020-09574-5
4. Oliveira CLP, Boulé NG, Sharma AM, Elliott SA, Siervo M, et al. (2021) A high-protein total diet replacement increases energy expenditure and leads to negative fat balance in healthy, normal-weight adults. Am J Clin Nutr 113: 476-487. https://doi.org/10.1093/ajcn/nqaa283
5. Gosby AK, Conigrave AD, Raubenheimer D, Simpson SJ (2014) Protein leverage and energy intake. Obes Rev 15: 183-191. https://doi.org/10.1111/obr.12131
6. Raubenheimer D, Simpson SJ (2019) Protein leverage: theoretical foundations and ten points of clarification. Obesity 27: 1225-1238. https://doi.org/10.1002/oby.22531
7. Saner C, Senior AM, Zhang H, Eloranta AM, Magnussen CG, et al. (2023) Evidence for protein leverage in a general population sample of children and adolescents. Eur J Clin Nutr 77: 652-659. https://doi.org/10.1038/s41430-023-01276-w
8. Grech A, Sui Z, Rangan A, Simpson SJ, Coogan SC, et al. (2022) Macronutrient (im)balance drives energy intake in an obesogenic food environment: an ecological analysis. Obesity 30: 2156-2166. https://doi.org/10.1002/oby.23578
9. Eglseer D, Traxler M, Schoufour JD, Weijs PJ, Voortman T, et al. (2023) Nutritional and exercise interventions in individuals with sarcopenic obesity around retirement age: a systematic review and meta-analysis. Nutr Rev 81: 1077-1090. https://doi.org/10.1093/nutrit/nuad007
10. Giglio BM, Lobo PCB, Pimentel GD (2023) Effects of whey protein supplementation on adiposity, body weight, and glycemic parameters: a synthesis of evidence. Nutr Metab Cardiovasc Dis 33: 258-274. https://doi.org/10.1016/j.numecd.2022.09.014
11. Rai C, Priyadarshini P (2023) Whey protein hydrolysates improve high-fat-diet-induced obesity by modulating the brain-peripheral axis of GLP-1 through inhibition of DPP-4 function in mice. Eur J Nutr 62: 2489-2507. https://doi.org/10.1007/s00394-023-03162-4
12. Zhong W, Wang H, Yang Y, Zhang Y, Lai H, et al. (2022) High-protein diet prevents fat mass increase after dieting by counteracting *Lactobacillus*-enhanced lipid absorption. Nat Metab 4: 1713-1731. https://doi.org/10.1038/s42255-022-00687-6
13. Totzauer M, Escribano J, Closa-Monasterolo R, Luque V, Verduci E, et al. (2022) Different protein intake in the first year and its effects on adiposity rebound and obesity throughout childhood: 11 years follow-up of a randomized controlled trial. Pediatr Obes 17: e12961. https://doi.org/10.1111/ijpo.12961
14. Guillet C, Masgrau A, Mishellany-Dutour A, Blot A, Caille A, et al. (2020) Bariatric surgery affects obesity-related protein requirements. Clin Nutr ESPEN 40: 392-400. https://doi.org/10.1016/j.clnesp.2020.06.007
15. Henderson GC, Nadeau D, Horton ES, Nair KS (2010) Effects of adiposity and 30 days of caloric restriction upon protein metabolism in moderately vs. severely obese women. Obesity 18: 1135-1142. https://doi.org/10.1038/oby.2009.505
16. Simonson M, Boirie Y, Guillet C (2020) Protein, amino acids and obesity treatment. Rev Endocr Metab Disord 21: 341-353. https://doi.org/10.1007/s11154-020-09574-5
17. Wu X, Xu M, Geng M, Chen S, Little PJ, et al. (2023) Targeting protein modifications in metabolic diseases: molecular mechanisms and targeted therapies. Sig Transduct Target Ther 8: 1-45. https://doi.org/10.1038/s41392-023-01439-y
18. White PJ, McGarrah RW, Herman MA, Bain JR, Shah SH, et al. (2021) Insulin action, type 2 diabetes, and branched-chain amino acids: a two-way street. Mol Metab 52: 101261. https://doi.org/10.1016/j.molmet.2021.101261
19. Dimou A, Tsimihodimos V, Bairaktari E (2022) The critical role of the branched chain amino acids (BCAAs) catabolism-regulating enzymes, branched-chain aminotransferase (BCAT) and branched-chain α-keto acid dehydrogenase (BCKD), in human pathophysiology. Int J Mol Sci 23: 4022. https://doi.org/10.3390/ijms23074022
20. De Bandt JP, Coumoul X, Barouki R (2022) Branched-chain amino acids and insulin resistance, from protein supply to diet-induced obesity. Nutrients 15: 68. https://doi.org/10.3390/nu15010068
21. Blair MC, Neinast MD, Jang C, Chu Q, Jung JW, et al. (2023) Branched-chain amino acid catabolism in muscle affects systemic BCAA levels but not insulin resistance. Nat Metab 5: 589-606. https://doi.org/10.1038/s42255-023-00794-y
22. Hædersdal S, Andersen A, Knop FK, Vilsbøll T (2023) Revisiting the role of glucagon in health, diabetes mellitus and other metabolic diseases. Nat Rev Endocrinol 19: 321-335. https://doi.org/10.1038/s41574-023-00817-4
23. Suppli MP, Bagger JI, Lund A, Demant M, Van Hall G, et al. (2020) Glucagon resistance at the level of amino acid turnover in obese subjects with hepatic steatosis. Diabetes 69: 1090-1099. https://doi.org/10.2337/db19-0715
24. Alves A, Morio B (2023) Alterations in glycine metabolism in obesity and chronic metabolic diseases - an update on new advances. Curr Opin Clin Nutr Metab Care 26: 50-54. https://doi.org/10.1097/mco.0000000000000883

25. Tan HC, Hsu JW, Tai ES, Chacko S, Wu V, et al. (2022) *De novo* glycine synthesis is reduced in adults with morbid obesity and increases following bariatric surgery. Front Endocrinol 13: 1-14. https://doi.org/10.3389/fendo.2022.900343

26. Nosworthy MG, Medina G, Lu ZH, House JD (2023) Plant proteins: methods of quality assessment and the human health benefits of pulses. Foods 12: 2816. https://doi.org/10.3390/foods12152816

27. Le Couteur DG, Handelsman DJ, Stanaway F, Waite LM, Blyth FM, et al. (2021) Sarcopenic obesity and amino acids: concord health and ageing in men project. J Gerontol Series A 76: 1000-1004. https://doi.org/10.1093/gerona/glab076

28. Steenackers N, Gesquiere I, Matthys C (2018) The relevance of dietary protein after bariatric surgery: what do we know? Curr Opin Clin Nutr Metab Care 21: 58-63. https://doi.org/10.1097/mco.0000000000000437

29. Romeijn MM, Holthuijsen DDB, Kolen AM, Janssen L, Schep G, et al. (2021) The effect of additional protein on lean body mass preservation in post-bariatric surgery patients: a systematic review. Nutr J 20: 1-9. https://doi.org/10.1186/s12937-021-00688-3

30. Ho C, Samwil SNM, Kahairudin Z, Jamhuri N (2023) Pre-habilitation with exercise and high whey-protein-based meal replacement therapy promotes weight loss and preserve muscle mass before bariatric surgery. Asian J Surg 46: 3716-3721. https://doi.org/10.1016/j.asjsur.2023.03.026

31. Yeung KTD, Penney N, Whiley L, Ashrafian H, Lewis MR, et al. (2022) The impact of bariatric surgery on serum tryptophan-kynurenine pathway metabolites. Sci Rep 12: 294. https://doi.org/10.1038/s41598-021-03833-4

32. Chen KY, Brychta RJ, Sater ZA, Cassimatis TM, Cero C, et al. (2020) Opportunities and challenges in the therapeutic activation of human energy expenditure and thermogenesis to manage obesity. J Bio Chem 295: 1926-1942. https://doi.org/10.1074/jbc.rev119.007363

33. Yokogoshi H, Ashida K (1975) Comparison between the metabolic effects of tryptophan and histidine deficiencies in the rat. J Nutr 105: 550-556. https://doi.org/10.1093/jn/105.5.550

34. Cheng Y, Meng Q, Wang C, Li H, Huang Z, et al. (2010) Leucine deprivation decreases fat mass by stimulation of lipolysis in white adipose tissue and upregulation of uncoupling protein 1 (UCP1) in brown adipose tissue. Diabetes 59: 17-25. https://doi.org/10.2337/db09-0929

35. Du Y, Meng Q, Zhang Q, Guo F (2012) Isoleucine or valine deprivation stimulates fat loss via increasing energy expenditure and regulating lipid metabolism in WAT. Amino Acids 43: 725-734. https://doi.org/10.1007/s00726-011-1123-8

36. Yu D, Yang SE, Miller BR, Wisinski JA, Sherman DS, et al. (2018) Short-term methionine deprivation improves metabolic health via sexually dimorphic, mTORC1-independent mechanisms. FASEB J 32: 3471-3482. https://doi.org/10.1096/fj.201701211r

37. Xiao F, Du Y, Lv Z, Chen S, Zhu J, et al. (2016) Effects of essential amino acids on lipid metabolism in mice and humans. J Mol Endocrinol 57: 223-231. https://doi.org/10.1530/jme-16-0116

38. Zhu X, Krasnow SM, Roth-Carter QR, Levasseur PR, Braun TP, et al. (2012) Hypothalamic signaling in anorexia induced by indispensable amino acid deficiency. Am J Physiol Endocrinol Metab 303: E1446-E1458. https://doi.org/10.1152/ajpendo.00427.2012

39. Felig P, Marliss E, Cahill GF (1969) Plasma amino acid levels and insulin secretion in obesity. N Engl J Med 281: 811-816. https://doi.org/10.1056/nejm196910092811503

40. Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, et al. (2009) A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab 9: 311-326. https://doi.org/10.1016/j.cmet.2009.02.002

41. She P, Van Horn C, Reid T, Hutson SM, Cooney RN, et al. (2007) Obesity-related elevations in plasma leucine are associated with alterations in enzymes involved in branched-chain amino acid metabolism. Am J Physiol Endocrinol Metab 293: E1552-E1563. https://doi.org/10.1152/ajpendo.00134.2007

42. Orentreich N, Matias JR, DeFelice A, Zimmerman JA (1993) Low methionine ingestion by rats extends life span. J Nutr 123: 269-274.

43. Yang Y, Zhang Y, Xu Y, Luo T, Ge Y, et al. (2019) Dietary methionine restriction improves the gut microbiota and reduces intestinal permeability and inflammation in high-fat-fed mice. Food Funct 10: 5952-5968. https://doi.org/10.1039/c9fo00766k

44. Yang Y, Zhang J, Wu G, Sun J, Wang Y, et al. (2018) Dietary methionine restriction regulated energy and protein homeostasis by improving thyroid function in high fat diet mice. Food Funct 9: 3718-3731. https://doi.org/10.1039/c8fo00685g

45. Hasek BE, Stewart LK, Henagan TM, Boudrean A, Lenard NR, et al. (2010) Dietary methionine restriction enhances metabolic flexibility and increases uncoupled respiration in both fed and fasted states. Am J Physiol Regul Integr Comp Physiol 299: R728-R739. https://doi.org/10.1152/ajpregu.00837.2009

46. Malloy VL, Krajcik RA, Bailey SJ, Hristopoulos G, Plummer JD, et al. (2006) Methionine restriction decreases visceral fat mass and preserves insulin action in aging male Fischer 344 rats independent of energy restriction. Aging Cell 5: 305-314. https://doi.org/10.1111/j.1474-9726.2006.00220.x

47. Perrone CE, Mattocks DAL, Hristopoulos G, Plummer JD, Krajcik RA, et al. (2008) Methionine restriction effects on 11-HSD1 activity and lipogenic/lipolytic balance in F344 rat adipose tissue. J Lipid Res 49: 12-23. https://doi.org/10.1194/jlr.m700194-jlr200

48. Anthony TG, Morrison CD, Gettys TW (2013) Remodeling of lipid metabolism by dietary restriction of essential amino acids. Diabetes 62: 2635-2644. https://doi.org/10.2337/db12-1613

49. Green CL, Lamming DW (2019) Regulation of metabolic health by essential dietary amino acids. Mech Ageing Dev 177: 186-200. https://doi.org/10.1016/j.mad.2018.07.004

50. Jonsson WO, Margolies NS, Anthony TG (2019) Dietary sulfur amino acid restriction and the integrated stress response: mechanistic insights. Nutrients 11: 1349. https://doi.org/10.3390/nu11061349

51. Zhou X, He L, Wan D, Yang H, Yao K, et al. (2016) Methionine restriction on lipid metabolism and its possible mechanisms. Amino Acids 48: 1533-1540. https://doi.org/10.1007/s00726-016-2247-7

52. Cummings NE, Williams EM, Kasza I, Konon EN, Schaid MD, et al. (2018) Restoration of metabolic health by decreased consumption of branched-chain amino acids. J Physiol 596: 623-645. https://doi.org/10.1113/jp275075

53. Richardson NE, Konon EN, Schuster HS, Mitchell AT, Boyle C, et al. (2021) Lifelong restriction of dietary branched-chain amino acids has sex-specific benefits for frailty and lifespan in mice. Nat Aging 1: 73-86. https://doi.org/10.1038/s43587-020-00006-2

54. Lees EK, Banks R, Cook C, Hill S, Morrice N, et al. (2017) Direct comparison of methionine restriction with leucine restriction on the metabolic health of C57BL/6J mice. Sci Rep 7: 1-10. https://doi.org/10.1038/s41598-017-10381-3

55. Zhou Z, Yin H, Guo Y, Fang Y, Yuan F, et al. (2021) A fifty percent leucine-restricted diet reduces fat mass and improves glucose regulation. Nutr Metab 18: 1-12. https://doi.org/10.1186/s12986-021-00564-1

56. Wanders D, Stone KP, Dille K, Simon J, Pierse A, et al. (2015) Metabolic responses to dietary leucine restriction involve remodeling of adipose tissue and enhanced hepatic insulin signaling. Biofactors 41: 391-402. https://doi.org/10.1002/biof.1240

57. Zapata RC, Singh A, Ajdari NM, Chelikani PK (2018) Dietary tryptophan restriction dose-dependently modulates energy balance, gut hormones, and microbiota in obesity-prone rats. Obesity 26: 730-739. https://doi.org/10.1002/oby.22136

58. Kamata S, Yamamoto J, Kamijo K, Ochiai T, Morita T, et al. (2014) Dietary deprivation of each essential amino acid induces differential systemic adaptive responses in mice. Mol Nutr Food Res 58: 1309-1321. https://doi.org/10.1002/mnfr.201300758

59. Han L, Wu G, Feng C, Yang Y, Li B, et al. (2020) Dietary methionine restriction improves the impairment of cardiac function in middle-aged obese mice. Food Funct 11: 1764-1778. https://doi.org/10.1039/c9fo02819f

60. Lees EK, Krol E, Shearer K, Mody N, Gettys TW, et al. (2015) Effects of hepatic protein tyrosine phosphatase 1B and methionine restriction on hepatic and whole-body glucose and lipid metabolism in mice. Metabolism 64: 305-314. https://doi.org/10.1016/j.metabol.2014.10.038

61. Orgeron ML, Stone KP, Wanders D, Cortez CC, Van NT, et al. (2014) The impact of dietary methionine restriction on biomarkers of metabolic health. Prog Mol Biol Transl Sci 121: 351-376. https://doi.org/10.1016/b978-0-12-800101-1.00011-9

62. Harms M, Seale P (2013) Brown and beige fat: development, function and therapeutic potential. Nat Med 19: 1252-1263. https://doi.org/10.1038/nm.3361

63. Li L, Li B, Li M, Speakman JR (2019) Switching on the furnace: regulation of heat production in brown adipose tissue. Mol Aspects Med 68: 60-73. https://doi.org/10.1016/j.mam.2019.07.005

64. Rosen ED, Spiegelman BM (2014) What we talk about when we talk about fat. Cell 156: 20-44. https://doi.org/10.1016/j.cell.2013.12.012

65. Yuan F, Jiang H, Yin H, Jiang X, Jiao F, et al. (2020) Activation of GCN2/ATF4 signals in amygdalar PKC-δ neurons promotes WAT browning under leucine deprivation. Nat Commun 11: 2847. https://doi.org/10.1038/s41467-020-16662-2

66. Wanders D, Burk DH, Cortez CC, Van NT, Stone KP, et al. (2015) UCP1 is an essential mediator of the effects of methionine restriction on energy balance but not insulin sensitivity. FASEB J 29: 2603-2615. https://doi.org/10.1096/fj.14-270348

67. Barcena L, Quiros PM, Durand S, Mayoral P, Rodriguez F, et al. (2018) Methionine restriction extends lifespan in progeroid mice and alters lipid and bile acid metabolism. Cell Rep 24: 2392-2403. https://doi.org/10.1016/j.celrep.2018.07.089

68. Jais A, Bruning JC (2022) Arcuate nucleus-dependent regulation of metabolism—pathways to obesity and diabetes mellitus. Endocr Rev 43: 314-328. https://doi.org/10.1210/endrev/bnab025

69. Li RJW, Zhang SY, Lam TKT (2020) Interaction of glucose sensing and leptin action in the brain. Mol Metab 39: 101011. https://doi.org/10.1016/j.molmet.2020.101011

70. Myers MG, Olson DP (2012) Central nervous system control of metabolism. Nature 491: 357-363. https://doi.org/10.1038/nature11705

71. Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG (2000) Central nervous system control of food intake. Nature 404: 661-671. https://doi.org/10.1038/35007534

72. Woods SC, Seeley RJ, Cota D (2008) Regulation of food intake through hypothalamic signaling networks involving mTOR. Annu Rev Nutr 28: 295-311. https://doi.org/10.1146/annurev.nutr.28.061807.155505

73. Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW (2006) Central nervous system control of food intake and body weight. Nature 443: 289-295. https://doi.org/10.1038/nature05026

74. Tsang AH, Nuzzaci D, Darwish T, Samudrala H, Blouet C (2020) Nutrient sensing in the nucleus of the solitary tract mediates non-aversive suppression of feeding via inhibition of AgRP neurons. Mol Metab 42: 101070. https://doi.org/10.1016/j.molmet.2020.101070

75. Cannon B, Nedergaard J (2004) Brown adipose tissue: function and physiological significance. Physiol Rev 84: 277-359. https://doi.org/10.1152/physrev.00015.2003

76. Cheng Y, Zhang Q, Meng Q, Xia T, Huang Z, et al. (2011) Leucine deprivation stimulates fat loss via increasing CRH expression in the hypothalamus and activating the sympathetic nervous system. Mol Endocrinol 25: 1624-1635. https://doi.org/10.1210/me.2011-0028

77. Green CR, Wallace M, Divakaruni AS, Phillips SA, Murphy AN, et al. (2016) Branched-chain amino acid catabolism fuels adipocyte differentiation and lipogenesis. Nat Chem Biol 12: 15-21. https://doi.org/10.1038/nchembio.1961

78. Liu J, Yu K, Zhu W (2016) Amino acid sensing in the gut and its mediation in gut-brain signal transduction. Anim Nutr 2: 69-73. https://doi.org/10.1016/j.aninu.2016.03.007

79. Zhang P, McGrath BC, Reinert J, Olsen DS, Lei L, et al. (2002) The GCN2 eIF2alpha kinase is required for adaptation to amino acid deprivation in mice. Mol Cell Biol 22: 6681-6688. https://doi.org/10.1128/MCB.22.19.6681-6688.2002

80. Dever TE, Hinnebusch AG (2005) GCN2 whets the appetite for amino acids. Mol Cell 18: 141-142. https://doi.org/10.1016/j.molcel.2005.03.023

81. Leung PM, Rogers QR (1971) Importance of prepyriform cortex in food-intake response of rats to amino acids. Am J Physiol 221: 929-935. https://doi.org/10.1152/ajplegacy.1971.221.3.929

82. Russell MC, Koehnle TJ, Barrett JA, Blevins JE, Gietzen DW (2003) The rapid anorectic response to a threonine imbalanced diet is decreased by injection of threonine into the anterior piriform cortex of rats. Nutr Neurosci 6: 247-251. https://doi.org/10.1080/1028415031000151567

83. Hao S, Sharp JW, Ross-Inta CM, McDaniel BJ, Anthony TG, et al. (2005) Uncharged tRNA and sensing of amino acid deficiency in mammalian piriform cortex. Science 307: 1776-1778. https://doi.org/10.1126/science.1104882

84. Maurin AC, Benani A, Lorsignol A, Brenachot X, Parry L, et al. (2014) Hypothalamic eIF2alpha signaling regulates food intake. Cell Rep 6: 438-444. https://doi.org/10.1016/j.celrep.2014.01.006

85. Maurin AC, Jousse C, Averous J, Parry L, Bruhat A, et al. (2005) The GCN2 kinase biases feeding behavior to maintain amino acid homeostasis in omnivores. Cell Metab 1: 273-277. https://doi.org/10.1016/j.cmet.2005.03.004

86. Herbert SL, Ribeiro C (2014) Nutrition: rejection is the fly's protection. Curr Biol 24: R278-R280. https://doi.org/10.1016/j.cub.2014.02.043

87. Bjordal M, Arquier N, Kniazeff J, Pin JP, Leopold P (2014) Sensing of amino acids in a dopaminergic circuitry promotes rejection of an incomplete diet in Drosophila. Cell 156: 510-521. https://doi.org/10.1016/j.cell.2013.12.024

88. Larsen TM, Dalskov SM, Van Baak M, Jebb SA, Papadaki A, et al. (2010) Diets with high or low protein content and glycemic index for weight-loss maintenance. N Engl J Med 363: 2102-2113. https://doi.org/10.1056/nejmoa1007137