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Review Article

The Effect of Dietary Protein on Weight Loss, Satiety, and Appetite Hormone

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Abstract

Objective: Obesity becomes pandemic, jeopardizing about one third people`s health worldwide. No intervention is promising due to the limitations. Dietary protein has been found to have greater weight loss effect. In this review article, we will summarize this and explore the possible resolution to go.

Summary: (1) High protein-induced satiety with subsequent energy intake reduction was significant and associated with greater weight loss and weight maintenance; (2) The mechanisms are increased thermogenesis, protein quality, free fat mass, and appetite hormones; (3) The peripheral anorexigenic hormones GLP-1 and PYY, as well as orexigenic hormone ghrelin play very important role; (4) However, it warrants further studies to investigate which types of protein and how they are contributing differently during this process.

Main Message: High dietary protein has greater weight loss effect, via its impact on food intake, satiety and appetite hormones.

Keywords: Dietary Protein; Weight Loss; Satiety; Appetite Hormone

Introduction

Obesity becomes pandemic, jeopardizing about one third people`s health worldwide [1]. No intervention is promising due to the limitations: poor compliance for diet and excises, side effects of limited medications, complications of surgery and varying individual responses etc. Poor weight loss may also be due to that: even when energy intake is less than expenditure, there is sustained satiety in obese condition, which may be driven or regulated by appetite hormones [2]. Dietary protein may affect this process, amino acids are metabolic targets for satiety, food intake, and energy expenditure, and thus may be a target for weight loss [3,57]. In this review article, we will address the effect of dietary protein on satiety, food intake, and weight loss, as well as its potential mechanism as far as appetite hormones concerned.

Dietary protein and weight loss

The World Health Organization (WHO) recommended normal-protein diet contains 0.8–1.2 g protein/kg body weight (BW), and dietary protein supplies 15–30% of energy intake under normal condition. Studies suggested that body weight loss and subsequent maintenance was greater with high protein diet than others [4]. This may be due to the effects of high-protein diets on satiety and food intake. But it has been overlooked, as non-significant different weight loss was found with high-protein or high-carbohydrate diets in some studies. However, majority of the studies with a variety of high-protein diets suggested an improved body composition and metabolic profiles, as well as reduced food intake [5-7]. This was further confirmed by studies showing high-protein diet required to keep body weight from rebound[8, 9]. Although weight loss was similar with normal protein diet (0.8g/kg) and higher protein diet (1.2g/kg), the free fat mass (FFM) sparing effect was stronger in the high-protein diet, which prevented reduction of resting energy expenditure (REM) and thus maintained weight loss. Protein-induced satiety can be acute after a single meal, as well as chronic, presented as subsequent decrease of food intake, lasting from 1 to 6 days and up to 6 months [10,11].

Mechanisms are high protein diet-induced thermogenesis caused by augmented protein oxidation (thus increased amino acid concentrations), increased urea synthesis, gluconeogenesis, and ketogenesis (if low-carbohydrate is present) [12,13]. Complete dietary proteins reach a positive balance with more gluconeogenesis at a later time.

High protein diet-induced thermogenesis is related to the energy-required for food processes after eating. It is based on the ATP needed for metabolism. These were reported as 0 to 3% for fat, 5 to 10% for carbohydrate, and 20 to 30% for protein, and thus high dietary protein induces bigger thermic response [14,15]. An important factor is the digestion rate. Ingestion of digested protein such as whey results in a stronger increase of protein synthesis and oxidation than slowly digested protein such as casein, and therefore a greater thermogenesis and weight loss [16].

Low carbohydrate diet has been found to be more effective for weight loss [17]. However, it is generally high in protein as well. This brought the concern if decreased carbohydrate or increased protein promotes weight loss. A recent cross-sectional study suggested that high-protein diet had greater success and better weight-maintenance, compared with others, despite the fact that all four diets promote weight loss [18]. This is believed as satiety effect created by ketone bodies, and increased energy expenditure through augmented gluconeogenesis. However, very limited studies were done and the results were controversial.

Decreased fat intake with high-protein diet may affect weight loss, possibly via reducing energy density. However, this has not yet been confirmed from studies.

Furthermore, it has been shown that as an effect of body weight loss, lipids, insulin sensitivity, and blood pressure were all improved, which was found due to a big increase in energy expenditure with high-protein diet that may be driven by increased gluconeogenesis and/or ureagenesis. On the contrary, acidified amino acids seem increase blood pressure, especially in susceptible patients with renal insufficiency, metabolic syndrome and type 2 diabetes (T2DM).

Yet, this may vary among different types of proteins. Moreover, caution of high protein intake should be paid in patients with renal insufficiency. However, no study supported the correlation between protein intake and renal disorders in healthy volunteers.

Overall, this weight loss effect of high dietary protein was facilitated by significant appetite hormone changes and satiety.

Dietary protein and satiety

It was showed that even short term high-protein diet can induce satiety. In some studies with healthy volunteers, a consistent elevated satiety by visual analogue scales (VAS) up to 60%-68% was demonstrated following a high protein diet, compared with 10-19% only in lower protein diets [19-21]. Additionally, only high-protein diet-induced satiety was associated with increased energy expenditure and reduced subsequent food intake, indicating that elevated oxygen consumption and body temperature lead to a sensation of oxygen deprivation and thus motivate satiety [22]. In these studies, the confounding factors were well controlled so that the possible differences between different forms of diets were limited as much as possible.

The quantities and qualities of the proteins as well as timing of consumption are all involved in suppressing hunger [23]. Protein quality is determined by its amino acid composition. This is the so-called aminostatic hypothesis, suggested by Mellinkoff in 1956 [16,24]. Appetite diminishes with amino acid infusion or protein consumption and regains as amino acid concentration drop. Some proteins are low in quality, because they are insufficient with essential amino acids (EAA). Gelatin is a low quality protein, because it is lacking tryptophan and low in other essential amino acids. Study showed that both gelatin and gelatin with added TRP suppress hunger much more than other proteins in casein, soya, whey, or whey without TRP, suggesting its satiety effect. The sensor for EAA level is located at anterior piriform cortex and projected to other brain areas associated with food intake. A low quality protein may induce a signal to stop eating. Gelatin-induced satiety and decreased food intake may serve as a signal for suppressing hunger instead of a satiety signal. Lang et al. did not reveal differences in food intake at dinner 8 hours after a high single protein lunch [25]. But these were not representative for the reality as most of the time people consumed mixed protein diet and the dinner was not that far from lunch. Other study investigating a short period (such as 90 minutes) after deal didn`t suggest the difference *either* [26]. And this may be due to so short period of time.

Another possibility is ketogenic state induced appetite suppression [27]. A high-protein low-carbohydrate diet induced increased fatty acid oxidation (FAO) and produced more ketone bodies. Increased fatty acid oxidation reduces appetite, which may be through activation of carnitinepalmitoyl transferase-1 (CPT-1), a rate-limiting step in FAO. β-Hydroxybutyrate is the most important ketone body in the circulation and was found to decrease food intake in rats. High-protein diets rich in ketogenic amino acids may cause increased ketone body levels in circulation, which may result in elevated satiety. High leucine and lysine proteins such as whey were reported to augment satiety as well.

However, more studies are warranted with variety of types of proteins, in overweight subjects with all different levels of energy balances.

More mechanism may be involved. Studies [28] suggested that a high-protein diet regulated satiety via modulating glucagon like peptide (GLP-1) and other appetite hormones such as peptide-YY (PYY) and ghrelin etc.

Dietary protein and appetite hormones

Feeding behavior is regulated by a variety of hormonal and neural signals. Hypothalamus is the major central nervous system (CNS) regulating dietary intake through modulating a variety of orexigenic and anoregenic peptides [29,30]. A main region is Arcuate (ARC). ARC-median eminence area is an entry for peripheral peptides such as insulin and leptin. ARC contains neurons expressing NPY, AGRP and POMC. Another major region is paraventricular nucleus (PVN), a main site for corticotropin releasing hormone (CRH), thyrotropin releasing hormone (TRH), NPY, Orexins, α-MSH and galanin. Ventromedial nucleus of hypothalamus (VMH) acts as satiety center and a key target for leptin. Dorsomedial hypothalamic nucleus (DMH) has connections with other nuclei and hypothalamus and thus serves for integrating and processing of information from these nuclei. Lateral hypothalamic area (LHA) is the classical feeding center having glucose-sensitive neurons stimulated by hypoglycemia. There are also extensive connections between hypothalamus and brainstem, especially the Nucleus of Tractus Solitarius (NTS), which has a high density of NPY-binding sites. The brainstem plays a role in individual meal size, increasing it when the meal frequency drops. Many neuro-peptides such as melanocortins, melanin concentrating hormone (MCH), neuropeptide Y (NPY), cocaine and amphetamine regulated transcript (CART), agouti-related peptide (AGRP), and orexins have been identified in animal models. In the peripheral circulation, ghrelin, peptide YY (PYY3-36), GLP-1, amylin, cholecystokinin (CCK), and bombesin regulate gastrointestinal motility, secretion, and absorption, and thus provide feedback to CNS regulating energy intake. Other peripheral hormones such as leptin and insulin also play very important role, via its regulation on hypothalamic appetite and offer critical targets for obesity management and provide a great potential for their clinical use in the near future.

It appeared that the higher dietary protein, the more satiety, driven by elevated plasma amino acid and changed appetite hormones, such as orexigenic hormone ghrelin and anorexigenic hormones GLP-1 and PYY etc. Limited studies showed the effects of anorexigenic and orexigenic hormones during high-protein-induced satiety. Yet, it is suggested that protein-induced satiety was concomitant with increased anorexigenic hormones such as GLP-1 and PYY release as well as decreased ghrelin [31]. However, there are controversial reports. There is very limited data on other hormones. As peripheral hormones may be easier targets for pharmaceutical strategy, in this review article, we will focus on the peripheral anorexigenic and orexigenic hormones.

GLP-1 response is nutrient related and satiety associated, because that high protein stimulated higher satiety but not higher GLP-1 release, whereas adequate protein with high carbohydrate has a lower satiety but higher GLP-1 release [32,33]. The α-cells of pancreas, L cells of gut, and neurons of brain stem nucleus are the major sources of glucagon precursor. There are two forms, GLP-1 (7–36 amide) and GLP-2, both involved in gastric emptying, food intake modification and body weight adjustment [34]. GLP-1 inhibits gastric emptying, hunger and food intake in man via PVN. GLP-1 antagonist blocked leptin-induced inhibition of food intake and body weight [35], suggesting that GLP-1 may be one target for the anorectic effects of leptin. GLP-2 may have overlapped effect with GLP-1. Veldhorst did report that high dietary protein were associated with increased GLP-1 and insulin but decreased ghrelin, none of which were related to satiety or subsequent food intake [36].

The PYY changes induced by high-protein diet were observed in variety of subjects, some are healthy volunteers and others are overweight or obese. Peptide YY (PYY) is a member of PP-fold peptide family, sharing homology of the sequence and is rich in tyrosine. It is synthesized by intestinal L-cells and circulates in two forms as inactive PYY_{1-36} and major active PYY_{3-36} [37]. After eating, PYY releases and peaks around 1–2 h, proportional to meal energy content, highest with fat. PYY causes delayed gastric emptying and secretion of pancreas and stomach, increases absorption, and thus inhibits daily food intake and causes weight loss, via its binding to Y2 receptor, inhibiting NPY neurons, and a reciprocal stimulation of POMC neurons on hypothalamic circuits. Its effect on appetite may relay on environmental stress, which can reduce in food intake on its own. A single infusion of PYY_{3-36} in healthy volunteers showed its inhibitory effects on appetite with a 30% reduction in food intake, accompanied by a reduction in hunger without changes of gastric emptying for up to 12 hours after the infusion was terminated, suggesting PYY_{3-36} may be an important signal for post-prandial satiety [38]. Obese and overweight patients have a low PYY level and deficient in post-prandial secretion, even maintaining sensitivity to exogenous PYY use. After jejunoileal bypass or vertical-banded gastroplasty, obese patients have increased PYY levels, which may suppress their appetite. Therefore, administration of PYY_{3-36} may be an effective strategy in treating obesity.

With high-protein breakfast, there was a greater reduction of ghrelin, compared with normal protein one, without correlation with satiety or subsequent food intake [39,40]. Orexigenic hormones could be a nutrient-specific support of satiety although non-linear relationships were observed. Ghrelin, a peptide of 28-amino

acid, is mainly produced in endocrine cells of the human gastric mucosa, but it was also found in several other tissues, and the only known orexigenic hormone so far. Its receptor is the family of 7-transmembrane G-protein receptors, which are predominantly detected in the pituitary and at lower levels in hypothalamus, stomach, heart, gut, and adipose tissues. Due to the widespread distribution of ghrelin and its receptor, it has many effects: it stimulates the release of growth hormone in the pituitary (due to its action on Growth hormone secretagogue receptor (GHS-R)) and induces a rise in the serum concentration of ACTH, cortisol, aldosterone, catecholamines and prolactin [41]. The high levels of ghrelin expressed in stomach led to the recognition of its central role in the regulation of appetite, body adiposity and energy balance. Ghrelin causes an increase of food intake and body weight, by stimulating the production of neuropeptide Y (NPY) and agouti-related protein (AGP) in the arcuate nucleus as well as antagonizes the leptin-induced inhibition of food intake [42]. ICV and peripheral administration of ghrelin to rodents caused a dose-dependent increase in food intake and body weight coupled to a reduction in fat utilization. Furthermore, ghrelin failed to induce adiposity in rats without hypothalamus. In humans, ghrelin levels increase during fasting and decrease following feeding, serving as a signal for meal initiation. Ghrelin levels are decreased in obese subjects and are markedly raised in patients with anorexia nervosa [43]. However, other factors besides body composition may impact ghrelin levels since significant decrease in plasma ghrelin levels are observed in anorexic patients even before the changes in the body mass index appear. It is apparent that ghrelin plays an important role in both acute and long-term control of energy balance and is also influenced by behavioral parameters although there were controversial reports. Thus, ghrelin may be regarded as a thrifty gene product that evolved to help animals consume fat, enhancing their survival during starvation.

During body weight rebound, leptin increased slower with high-protein diet. When energy storage is low, leptin concentration falls, stimulating neuropeptide Y (NPY), galanin and agouti-related protein (AGRP) and reducing α-melanocyte-stimulating hormone (α-MSH), cocaine and amphetamine-regulated transcript (CART) [44]. Leptin was produced in adipose tissue, heart, bone, cartilage and brain, coded by ob gene. Mutation or depletion of leptin results in obesity, which can be controlled with leptin administration. One or more leptin receptors were found in many tissues, some of them are cytokines activated by JAK-STAT signaling pathway. The long-form receptor Ob-Rb is found in ARC, PVN, DMH and LHA of hypothalamus and is necessary for leptin`s effect on appetite. Leptin inhibits orexigenic peptides such as NPY, MCH, orexins and AGRP, and stimulates anorectic peptides such as α-MSH,CART and CRH, and thus decrease body weight [45].

CCK levels predicted satiety in females not in males. Cholecystokinin (CCK) is a peptide in gastrointestinal tract and brain sites such as LH, NTS, medial pons and lateral medulla, presented in many forms, including CCK-58, CCK-33 and CCK-8 [46]. In response to nutrients, CCK is rapidly released to circulation and remains up to 5 h, being involved in reward behavior, memory, anxiety, and satiety through stimulating secretion from pancreas, contraction of gall bladder, motility of intestine, memory enhancement and inhibition of gastric motility [47]. CCK also controls meal size, by its endocrine actions in intestines and paracrine and neurocrine actions in the brain, after binding to its receptors (CCKr). The satiety actions of CCK are mediated by CCK-A receptors via a neurocrine or paracrine action, suggesting that CCK has a direct effect on food intake via activation of CCK-A receptors located at vagal afferent neurons [48]. Yet, the duration of effect is short, because its half-life is only 1–2 min. It was suggested that there is a synergistic effect between leptin and CCK and CCK may contribute to long-term control of food intake and body weight when leptin in the brain is elevated [48]. However, Burton-Freeman`s study suggested that CCK predicted satiety in women but not in men, following a high protein diet, and there was no relationship between satiety, subsequent food intake and appetite hormone responses [49].

Amylin is a peptide of 37 amino acids, and a member of the family of calcitonin gene-related peptide (CGRP) and calcitonin (CT) [50]. In response to food, amylin is released from pancreatic β-cells concomitantly with insulin and has an anorectic effect, via its peripheral and central effects as well as slowing gastric emptying. Amylin seems to decrease food intake is by enhancing actions of other peptides such as CCK, glucagon, and bombesin, all of which in turn increase amylin secretion [51]. Amylin is rapidly released during meals, leading to a dose-related meal size reduction, with a short duration. Area postrema (AP) plays a predominant role in amylin's satiating effect, through activation of AP neurons. Nucleus of the solitary tract (NTS) relays this effect to higher brain structures, lateral parabrachial nucleus, central nucleus of the amygdala, and the bed nucleus of the striaterminalis. Furthermore, amylin's anorectic effect may be due to reduced orexigenic neuropeptides in lateral hypothalamus. Amylin may also exert its effects viaserotonergic, histaminergic, and dopaminergic D2 systems. Preclinical and clinical studies with pramlintide (a human amylin analogue) led to weight loss, supporting the role of amylin in satiety [52].

Insulin is a major metabolic hormone produced by the pancreas and the first adiposity signal to be described. Its level varies with adiposity, which increases during positive energy balance and decreases during negative energy balance. After a meal, insulin rapidly secret and enters the brain, where it functions as an anorexigenic signal. Its receptors are widely distributed in the brain sites such as olfactory bulbs, arcuate nucleus, DMH, PVN, and suprachiasmatic and periventricular regions [53]. Several insulin receptor substrates (IRSs) including IRS-1 and IRS-2 have been identified in neurons. IRS-2 is highly expressed in ARC. IRS-2-knockout is associated with increased food intake and fat storage. Insulin and leptin, along with other cytokines were shown to share common intracellular signaling pathways through IRS and phoshoinositide3-kinase, leading to downstream signal transduction such as NPY and melanocortin systems, both of which regulate food intake and body weight.

Bombesin is a peptide of 14 amino acid derived from skin of European amphibian Bombinabombina. Bombesin-like peptides are neuromedin B (NMB) and gastrin-releasing peptide (GRP). Bombesin binds to G-protein coupled receptors and mediate their actions via phospholipase C. The receptors are BB1 (specific for NMB, NMB-R), BB2 (specific for GRP, GRP-R) and Bombesin receptor subtype 3 (BRS3), which are widely expressed in the CNS, gastrointestinal tract, and PVN of hypothalamus [54]. Bombesin, induced by gastric distension, may be a messenger for nervous center of satiety and suppress food intake, via regulating feeding behavior and metabolism [55]. Fluctuation with meals was reported in rats. PVN and the nucleus tractussolitarius (NTS) are especially sensitive to the feeding suppressant effects of bombesin. The feeding-suppressant effects of bombesin may be mediated via its interaction with CRF, CCK, leptin and MCH [56].

Conclusion

1. High protein-induced satiety with subsequent energy intake reduction was significant, which can last from 1-6 days up to 6 months and associated with greater weight loss and body weight maintenance thereafter;
2. The mechanisms may be involved are increased thermogenesis, quality of the protein, effect on free fat mass, and appetite hormones;
3. Among all the appetite hormones involved, the peripheral anorexigenic hormones GLP-1 and PYY, as well as orexigenic hormone ghrelin play very important role;
4. However, it warrants further studies to investigate which types of protein and how they are contributing differently during this process.

Conflict of Interest

The authors declared no conflict of interest.

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