

Review Article

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Effects of whey protein on appetite: An overview with a mechanistic insight

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Abstract

Objective: The present review summarizes current knowledge on the possible mechanisms of Whey Protein (WP) action on appetite.

Background: Due to the high prevalence of obesity worldwide and the relationship between obesity and Non communicable diseases (e.g., diabetes mellitus, cancer, and cardiovascular diseases), as the main cause of mortality, strategies for weight loss such as appetite reduction is important for increment of life expectancy and mortality reduction. Since several short-term studies and also a few long-term trials showed WP effect on appetite reduction, we reviewed the mechanisms of this action.

Methods: Recent publications on the effects of WP on appetite were searched and all proposed mechanisms of action were overviewed.

Discussion: WP affects on gut peptides such as ghrelin, Glucose-Dependent Insulinotropic Polypeptide (GIP), Glucagon-Like Peptide-1 (GLP-1), Peptide YY (PYY), and Cholecystokinin (CCK) and regulates the appetite by stimulation or suppression of these peptides' secretion. WP also reduces the gastric emptying rate and increases the satiety duration. In addition, after WP digestion, circulating Amino Acids (AAs) could suppress the appetite via vagal feedback and also direct effect at the level of the hypothalamus.

Conclusion: The major WP's mechanisms of action on appetite reduction include (I) effects of WP on gut peptides; (II) WP effects on gastric emptying and absorption rate; and (III) effects of WP on vagal feedback and direct suppression of hunger at the level of the hypothalamus. Further precise studies on the relationships between different brain areas, and different neural circuits' adaptations after the ingestion of WP are recommended.

Keywords: Appetite; Gastric emptying; Glucagon-like peptide 1; Hypothalamus; Whey protein.

Introduction

The major cause of mortality and premature disability include Non Communicable Diseases (NCDs) such as diabetes mellitus, cancer, and cardiovascular diseases. Since obesity is the main risk factor for NCDs [1], the approaches for reduction of obesity prevalence are appropriate ways to increase life expectancy and decrease mortality worldwide. Given that the imbalance between energy expenditure and energy intake leads to obesity, reduction of appetite could be beneficial for weight management [1].

Due to the more satiety effect of protein in comparison with other macronutrients, and considering that protein supplements are often rich in Whey Protein (WP) [2,3], supplementation with WP could be effective for appetite regulation. There is about 3.5 gram protein in 100 ml of cow milk; WP comprises about 20% and casein accounts for about 80% of the total protein in milk [4]. WP contain the following essential amino acid profile measured in mg/g of protein: leucine, 105 mg; lysine, 93 mg; tyrosine, 32 mg; cysteine, 21 mg; isoleucine, 63 mg; valine, 58 mg; threonine, 69 mg, tryptophan, 18 mg; histidine, 17 mg [5].

According to the results of a meta-analysis of Randomized Controlled Trials (RCTs) on WP supplementation effects on appetite, a significant reduction in short-term appetite has been reported [6]. Even appetite suppression has been shown after consumption of biscuits fortified with WP for eight weeks [5]. Because of the importance of appetite regulation in overweight and obese individuals, in the present article, we reviewed WP's possible mechanisms of action on appetite.

Effects on gut peptides

Some physiologic factors are responsible for body weight maintenance via short and long-term regulatory systems. In response to food intake, peripheral hormones such as leptin and insulin, as well as gastrointestinal hormones such as ghrelin, Glucose-Dependent Insulinotropic Polypeptide (GIP), Glucagon-Like Peptide-1 (GLP-1), peptide YY (PYY), and Cholecystokinin (CCK), are secreted and regulate body weight. These hormones regulate appetite and metabolism by signaling the hypothalamus and activating or deactivating hypothalamic nuclei neurons [7].

GLP-1: GLP-1 is a 30-amino acid peptide hormone produced by intestinal epithelial endocrine L-cells. The stimuli and molecular mechanisms involved in the release of GLP-1 in response to meal intake are discussed. GLP-1's primary actions are stimulating insulin secretion (as an incretin hormone) and inhibiting glucagon secretion, thereby helping to limit postprandial glucose levels. It also inhibits gastrointestinal motility and secretion, acting as an enterogastrone and a component of the "ileal brake" mechanism. GLP-1 appears to be a physiological regulator of appetite and food consumption as well [8].

It was confirmed that a combination of essential amino acids and Branched Chain Amino Acids (BCAAs) leucine and isoleucine can effectively trigger the release of GLP-1 from a human intestinal cell line. As WP is rich in BCAAs, its consumption could be effective to increase GLP-1 level [5].

CCK: A peptide distributed widely throughout the gastroin-

testinal tract and the central nervous system, has several physiological effects including the stimulation of gallbladder contraction and pancreatic and gastric acid secretion, slowing gastric emptying, and suppression of energy intake [9]. Giezenaar et al., concluded that a 70 g WP (280 kcal) drink was associated with a slower gastric emptying time, lower ghrelin, and higher CCK concentrations [10].

GIP: GIP regulates blood glucose levels by acting on the pancreas in an insulinotropic manner. GIP activates lipoprotein lipase, stimulates fatty acid and glucose uptake, and promotes lipid synthesis in cultured adipocytes. These findings are consistent with human studies in which GIP has been shown to promote lipid storage by increasing adipose tissue blood flow and triglyceride uptake. WP may help in decreasing food intake by preserving GIP [11].

Leptin: Leptin is a mediator of long-term regulation of energy balance, suppressing food intake and thereby inducing weight loss. Adipose tissue is the primary source of leptin. Leptin is produced in small amounts in other human tissues besides adipose tissue, including the stomach, mammary epithelium, placenta, and heart [12]. Hassanzadeh-Rostami et al. demonstrated that WP did not affect serum leptin levels. Some other studies also reported no significant results [13,14]. Similarly, despite decreasing body weight and fat, a high protein diet containing WP had no effect on serum leptin levels in rats [13]. Thus, the type of diet and amount of fat consumed is more likely to be related to leptin than adding protein [5].

Uroguanylin: Prouroguanylin is a prohormone and gastrointestinal paracrine signal that is secreted after nutrient ingestion. In the CNS, prouroguanylin is converted to uroguanylin, which can activate GUCY2C receptors in the brain to reduce food intake in mice [15]. This 16-amino acid residue peptide is a novel component of the gut-brain axis, presenting a novel and one-of-a-kind opportunity to manipulate gut-brain signaling for therapeutic intervention in obesity. The identification of uroguanylin as a satiety factor adds to the list of post-translational strategies used by the GI tract to send afferent signals to the brain to maintain metabolic homeostasis. The hormonally inactive prouroguanylin seems to be secreted and transported to the CNS after meals via blood circulation, where it is converted to the active hormone, activates its cognate receptor, and reduces appetite [12]. Despite the effects of uroguanylin on appetite, we couldn't find any study on the effects of WP on this peptide.

Ghrelin: Ghrelin which is well-known as the "hunger hormone", was first identified through its receptor, the Growth Hormone Secretagogue Receptor (GHS-R), before elucidating its function as a peptide that releases growth hormone. However, until research showed a correlation between an increase in plasma levels of ghrelin before meals and a subsequent decrease in plasma levels of ghrelin after meals, the role of this hormone in regulating appetite and satiety was not explicitly known. Ghrelin and leptin signals work together to regulate our feelings of hunger and satiety by sending signals to different hypothalamic nuclei. Imbalances and dysregulation of these hormones can have serious consequences on the body's energy homeostasis. Astbury et al., discovered that ghrelin levels decreased after consuming a snack bar containing WP and polydextrose [16]. Other studies that looked at the acute effects of

WP, presented the same result [17] that shows the effect of WP on decreasing ghrelin hormone and appetite [10].

Gastric emptying and absorption rate

Since the gut is the first and most important organ in which food is processed, it is designed to recognize meal volume and composition and thus plays an important role in appetite regulation. The distension of the stomach during and after food intake is important in determining appetite. However, after the lag phase of gastric emptying, when the stomach gradually empties into the small intestine, the stomach's distension decreases, and it is thus likely to play a gradually decreasing role in satiety signaling. The emphasis shifts to satiety mechanisms that are controlled by gastric emptying rate: nutrient intravenous exposure [18]. In a study designed by Ma et al. eight patients with type 2 diabetes (T2D) were given 350 mL of beef soup 30 minutes before a potato meal; either the soup (whey preload) or the potato (whey in meal) or no whey was given. After the whey preload, gastric emptying was the slowest ($P < 0.0005$) [19]. WP consumed before a carbohydrate meal can increase insulin and incretin hormone secretion as well as slow gastric emptying, resulting in a significant reduction in postprandial glycemia in T2D. Ma et al. found that giving WP before or with a high-carbohydrate meal reduced postprandial glycemia significantly in diet-controlled patients with T2D [19].

In another study conducted by Elovärilä et al., gastric emptying was analyzed by 3D ultrasonography with the use of a Logiq 9 ultrasound system (GE Health Care Technologies, Milwaukee, WI, USA) with TruScan Architecture (a built-in magnetic sensor for 3D image acquisitions) and conclude that When increasing loads of WP (i.e., 8, 24, and 48 g) were delivered into the duodenum at rates mimicking the normal range of gastric emptying (i.e., 1-4 kcal/min), postprandial plasma concentrations of 19 out of 20 amino acids increased in a load-of-protein dependent manner [20].

Vagal feedback and direct suppression of hunger at the level of the hypothalamus

After the digestion of WP, circulating Amino Acids (AAs) affect the central nervous system via (I) the gut-brain axis (the vagus nerve to the brainstem); and (II) direct effect on the hypothalamus and brainstem [21,22]. Electrophysiological recordings showed that vagal afferent fibers were activated by hepatic portal vein perfusion of amino acids which, supports the role of hepatic portal vein vagal afferents in signaling to the brain after protein ingestion [23].

The hypothalamus, an area of brain with a role in food intake control, has many nuclei including the Arcuate Nucleus (ARC), the Paraventricular Nucleus (PVN), the ventromedial nucleus, the dorsomedial nucleus, and the lateral hypothalamic area. These nuclei contain energy homeostasis-regulating circuits [24]. In the ARC, a reduction in food intake is induced by Pro-Opiomelanocortin (POMC) neuron activation and activation of Neuropeptide Y (NPY)/ Agouti-Related Peptide (AgRP) neurons induce an increase in food intake [25]. The main role of WP in appetite suppression at the level of the hypothalamus is related to its high content of BCAAs [26]. Ingestion of WP or the intracerebroventricular administration of BCAAs suppresses AMP-Activated Protein Kinase (AMPK) phosphorylation and activates the Mammalian Target Of Rapamycin (mTOR) in the hypothalamus [27,28]. Finally, mTOR activation and AMPK phosphorylation suppression lead to a reduction of orexigenic NPY and AgRP

neuropeptides levels and increment of the expression of POMC that has an anorexigenic effect [27,28].

Conclusion

Several short-term studies and also a few long-term trials demonstrated that WP could reduce appetite. In the present review, we summarized the evidence of WP's effects on appetite with a mechanistic insight. The main WP's possible mechanisms of action on appetite regulation are as follow; (I) effects of WP on gut peptides such as CCK, GLP-1, GIP, leptin, and ghrelin; (II) WP effects on gastric emptying and absorption rate; and (III) effects of WP on vagal feedback and direct suppression of hunger at the level of the hypothalamus.

The relationships between different brain areas, and different neural circuits adaptations after the ingestion of WP should be studied more precisely in future studies.

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