Novel Molecules Regulating Energy Homeostasis: Physiology and Regulation by Macronutrient Intake and Weight Loss

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Excess energy intake, without a compensatory increase of energy expenditure, leads to obesity. Several molecules are involved in energy homeostasis regulation and new ones are being discovered constantly. Appetite regulating hormones such as ghrelin, peptide tyrosine-tyrosine and amylin or incretins such as the gastric inhibitory polypeptide have been studied extensively while other molecules such as fibroblast growth factor 21, chemerin, irisin, secreted frizzle-related protein-4, total bile acids, and heme oxygenase-1 have been linked to energy homeostasis regulation more recently and the specific role of each one of them has not been fully elucidated. This mini review focuses on the above mentioned molecules and discusses them in relation to their regulation by the macronutrient composition of the diet as well as diet-induced weight loss.

Keywords: Ghrelin; Peptide tyrosine-tyrosine; Islet amyloid polypeptide; Gastric inhibitory polypeptide; Fibroblast growth factor 21; Chemerin; Irisin

INTRODUCTION

Several molecules are involved in energy homeostasis regulation and new ones are being discovered constantly. The central nervous system (CNS) integrates information from the environment and the periphery to regulate energy homeostasis. Although in normal-weight people the system maintains a balance of energy homeostasis, the system fails in the two extremes, i.e., in obese as well as in extremely lean individuals (e.g., anorexia nervosa). The study of novel molecules involved in energy homeostasis is of utmost importance to shed more light in the mechanisms behind the observed imbalances.

NOVEL MOLECULES IMPORTANT IN ENERGY HOMEOSTASIS

Fibroblast growth factor 21 (FGF-21) was identified in 2000 [1]. It is a novel hepatokine that is involved in several metabolic pathways and in the regulation of adiposity in both animals and humans [2-7]. FGF-21 is an important molecule for energy homeostasis regulation as knock-out mice present mild weight gain, slightly impaired glucose homeostasis and tolerance after 24 hours fasting while they cannot effectively mobilize and utilize lipids after a ketogenic diet [8]. FGF-21 levels are increased in obesity and there is evidence of FGF-21 resistance in both...
obese animals and humans [2,9,10]. Its levels are reduced after weight loss with either caloric restriction or specific types of bariatric surgery in humans [11-13]. FGF-21 can induce weight loss in obese animals through stimulation of the sympathetic nerve activity into brown adipose tissue [14]. Macronutrient intake seems to affect FGF-21 levels. Specifically, in animal studies, a ketogenic diet, i.e., a high fat-low carbohydrate diet has been shown to increase FGF-21 expression and levels [15,16]. However this could, also, be attributed to the low protein content of this diet since a low protein diet leads to FGF-21 levels increase in both animals and humans compared to a control diet regardless of energy intake [17-19]. On the other hand, dietary manipulation (low or high carbohydrate diets) of the diet was not found to affect FGF-21 levels in humans [20]. In addition, FGF-21 could regulate macronutrient intake in humans as genome wide associations studies show that certain variants in the FGF-21 locus are associated with a reduced protein and/or lipid intake but with an increased carbohydrate intake [21,22]. Taken together, available evidence indicates that in humans caloric restriction reduces FGF-21 levels. Although a low-protein diet seems to increase the expression and concentrations of FGF-21 the effect of carbohydrates on FGF-21 levels still needs to be elucidated. More research is needed to explore how caloric restriction and/or macronutrient manipulation of the diet can affect FGF-21 levels and shed light into this field.

Chemerin is a novel chemoattractant adipokine and hepatokine, first characterized in 2003 [23]. Chemerin is involved in the regulation of many metabolic pathways including adipocyte and glucose metabolism, in adipogenesis and in immune responses [24-30]. Chemerin levels positively correlate with body mass index (BMI), fat mass, and several markers of inflammation and are elevated in obese individuals, in individuals with diabetes and also in prediabetic states [24,26,31-33]. Weight loss achieved either with hypocaloric diet or a combination of diet with exercise or bariatric surgery results in reductions of chemerin levels [33-39]. Significant reductions of chemerin levels can be observed either acutely, i.e., 24-hour postoperation or in the long-term, i.e., 6 or 12 months later [40]. Although chemerin concentrations decrease with weight loss, they may increase again with weight regain [41]. Energy deficit induced by exercise seems to result in greater chemerin level reductions in obese males compared to when the same energy deficit is induced by diet alone, probably due to the greater reduction in fat mass with the exercise program [42]. Macronutrient composition of the diet seems to affect chemerin levels. A high carbohydrate diet results in increased chemerin concentrations compared to a diet lower in carbohydrate content [43]. In another study a low carbohydrate diet did not result in significantly greater chemerin levels reductions compared to a low lipid diet or a Mediterranean diet [41]. To summarize, energy restriction reduces chemerin levels in humans and there is preliminary evidence that the macronutrient composition of the diet can affect chemerin concentrations with higher carbohydrate consumption resulting in an increase of its levels.

Irisin is a novel myokine that is considered a muscle-derived energy-expenditure signal secreted from the skeletal muscle after cleavage of the myokine fibronectin type III domain containing 5 (FNDC5) in response to exercise and/or peroxisome proliferator-activated receptor-γ coactivation 1a (PGC-1a) [44]. A diverse array of metabolic actions has been associated with irisin levels [45-66]. Irisin levels correlate positively with markers of adiposity, are increased in obesity and irisin resistance might develop in obese individuals [67-70]. In mice, recombinant irisin administration results in weight loss [71], while in humans, weight loss results in irisin levels reduction 6 months after bariatric surgery [64] or after a weight loss diet [72,73]. However, irisin concentrations increase again after weight regain [69]. In response to diet composition, irisin levels seem to be minimally affected. Specifically, in animals, circulating irisin levels remain unaffected by the fat content of the diet (high vs. low) [74]. Furthermore, irisin concentrations were equally reduced in humans after two weight loss diets differing in macronutrient composition followed for 8 weeks because of the energy restriction induced weight loss but were positively correlated with carbohydrate intake coming from cereals, pulses, fruit, and vegetables at the end of the 8 weeks intervention [63] and with prudent diets including the DASH (Dietary Approaches to Stop Hypertension) diet according to another study [75]. Other studies fail to support an association between irisin levels and diet quality or caloric intake [76,77]. Furthermore, supplementation with or without eicosapentaenoic acid and/or α-lipoic acid and/or both had no additional effect on the reduction of irisin levels after an energy restricted weight loss diet [78]. Although available data suggest a reduction of irisin levels in response to energy restriction, limited data exist regarding the effect of the macronutrient composition of the diet on its levels.

Secreted frizzle-related protein-4 (SFRP-4) is an adipokine that acts as an extracellular antagonist of the wingless-type mouse mammary tumor virus integration site family (WNT) signaling pathway [79]. SFRP-4 levels are increased in obesity and are associated with insulin resistance [80]. Diet induced
obese SFRP-4−/− mice on a high fat diet had reduced food intake and energy expenditure compared to their control littermates [81]. On the other hand, SFRP-4−/− mice on a chow diet presented normal food intake and energy expenditure [81]. However, since this is a pretty new field of investigation, way more research is needed to explore the effects of obesity, energy restriction, and weight loss as well as the macronutrient composition of the diet on SFRP-4 levels in both animals and humans.

Bile acids are involved in dietary lipid absorption and cholesterol catabolism but an emerging role of them as signaling molecules in energy homeostasis has also been indicated. Specifically, administration of bile acids to mice can prevent and reserve obesity but also can increases energy expenditure in brown adipose tissue [82]. The weight that mice on a high fat diet gained was reversed (reached same weight gain levels with chow-fed mice) by the supplementation of the high fat diet with cholic acid due to adipose mass and morphology prevention changes. In animal models, bariatric surgery alters bile flow and this is associated with an increase in bile acids and gut hormones inducing satiety as well as with a decrease in food intake and body weight [83-85]. In humans, bile acids in the plasma correlate positively with BMI and negatively with the cognitive restraint of eating in obese patients [86]. Levels of total bile acids increase either acutely or in the long-term after bariatric surgery regardless of energy restriction but in a type of surgery specific manner [87-90]. Fecal bile acid excretion is increased after bariatric surgery in a type of surgery specific manner, too [91]. This increase correlates with alterations in substrate oxidation [92], with increased peak postprandial plasma glucagon-like peptide-1 but not with resting energy expenditure [93]. On the other hand, diet-induced weight loss results in the reduction of blood levels of unconjugated bile acids or biliary bile acids without affecting total plasma bile acids [88,94]. Fecal bile acid excretion was also greater after weight loss [95]. In response to macronutrients, a high fat diet with high protein to carbohydrate ratio might be associated with increased bile acid production according to preliminary evidence in mice, but this warrants further investigation [96]. In addition, high fat diets result in greater fecal bile acid excretion compared to high carbohydrate diets in humans [97-99]. A low fat diet might change the proportion of specific bile acids in serum but since no weight change data were available to exclude as a mediating factor weight loss, results should be interpreted with caution [100]. In summary, bariatric surgery results in an increase of blood levels of bile acids which occurs independent of energy restriction, while limited data indicate that energy restriction does not affect circulating total bile acids concentrations. Data on the effect of macronutrient composition of the diet on bile acids blood levels is still lacking.

Heme oxygenase-1 (HO-1) is a stress-induced isozyme of HOs that catalyzes the metabolic conversion of heme to bile pigments, iron, and carbon monoxide affecting many important cellular functions such as inflammation, cellular proliferation, and apoptotic cell death [101,102]. In obesity, HO-1 is upregulated in adipose tissue and in macrophages mostly in the subcutaneous rather than in the visceral adipose tissue and this overexpression correlates negatively with the waist to hip ratio in humans [103,104]. In animals, the chronic induction of HO-1 results in body weight loss [105-110] while inhibition of HO-1 attenuates it [111]. Potential mechanisms for this decrease in body weight include but are not limited to the increase of O2 consumption, heat production, and locomotor activity [112] while a decrease in the food intake has not been fully proven but cannot be excluded. Furthermore, HO-1 could decrease the content of both visceral and subcutaneous adipose tissue and could ameliorate vascular and adipocyte dysfunction and inflammation occurring in diet-induced obesity [113-116]. However, HO-1 overexpression in adipocytes was not found to protect against high fat diet-induced obesity [117]. Since all these studies are animal studies and different HO-1 inducers/metabolites have been investigated, more research is needed to replicate these in humans. Furthermore, more research is needed to elucidate the effect of energy restriction and weight loss as well as the macronutrient composition of the diet on HO-1 levels.

Ghrelin is an orexigenic hormone of the periphery secreted by the stomach with several actions [118-121]. It is considered a meal initiator; its levels increase preprandially and fall postprandially [122] in proportion to the amount of calories consumed [123]. Fasting ghrelin levels are suppressed in obesity [124,125] and its responses to a meal are blunted in obese individuals [126,127]. Diet-induced weight loss results in the increase of fasting ghrelin levels [128,129]. The macronutrient composition of the diet affects ghrelin responses to a meal with a high carbohydrate and a high protein diet suppressing ghrelin levels to a greater extent than a high fat diet in both mice and humans [130-132]. Other studies have failed to show an effect of macronutrients [133,134]. Thus, weight gain and loss affect circulating ghrelin concentrations but since some inconsistences still exist regarding the effect of macronutrient composition of the diet on ghrelin levels, more studies will be a useful addition to the literature.

Peptide tyrosine-tyrosine (PYY) is an anorexigenic hormone

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produced by the L-cells of the distal gut that suppresses energy intake [119,135,136]. Its levels increase after meal intake in proportion to the caloric content of the meal and exogenous administration of PYY reduces food consumption [127,137]. It is not clear whether its fasting levels are decreased in obesity [125,127,137,138] or remain stable [139-141], but it seems that PYY level responses to a meal are attenuated [125,127,137,138]. Diet induced weight loss has been proposed to decrease PYY levels [140,142], but this is not supported by all studies [143-145]. The macronutrient composition of the diet seems to affect PYY levels, as well. All macronutrients can stimulate PYY release but lipids and protein trigger the greater responses [133,134,146-150]. Although research has shown that obesity, diet-induced weight loss, and macronutrient composition of the diet may affect PYY levels, mixed results still exist.

Amylin is a hormone co-stored and co-secreted with insulin from the pancreatic beta cells in response to nutrients [151]. Amylin can act as an anorexigenic factor/signal of satiation [152]. Central and peripheral amylin administration in animals reduces food intake and body weight as well as it slows gastric emptying in both animals and humans [153-157]. Amylin may have a synergistic effect in causing negative energy balance with leptin [155,156] and recently, it was suggested that endogenous ventromedial amylin signaling is essential for full leptin signaling in order to protect from diet-induced obesity [158]. Amylin levels are increased in obesity [157] and they fall after diet-induced weight loss in humans [142,159]. Furthermore, macronutrients seem to affect amylin levels which are triggered mostly by carbohydrate rather than lipid consumption in humans [160]. Amylin levels are affected by obesity and weight loss and may be also by the macronutrient composition of the diet but this remains to be confirmed.

Gastric inhibitory polypeptide (GIP) is an incretin secreted by the K-cells of the gastrointestinal track [161] following the ingestion of nutrients which stimulates insulin release [162-164]. Although it is not considered a main appetite regulating peptide, GIP might affect appetite indirectly through its insulin stimulating effects [165]. Exogenous administration of GIP in humans had no effect on appetite feelings but decreased gastric-half emptying time [166]. A null effect has also been reported by others for gastric emptying [167]. In obesity GIP levels are increased in the postprandial but not in the fasting state [168]. Diet-induced weight loss does not affect fasting GIP levels while it is unclear whether postprandial levels of GIP change or not [142,168,169]. Furthermore, weight regain after surgical weight loss does not change fasting GIP levels or responses compared to weight maintenance [170]. The macronutrient composition of the diet affects GIP responses which seem to be more sensitive to a high carbohydrate and a high fat diet [171,172], while a high glycemic-load diet seems to increase its levels, too [173]. Although GIP levels depend on nutrient intake, still it is not clear what is the effect of weight loss especially on its postprandial levels and thus further investigation is needed.

CONCLUSIONS

Available data indicate that diet-induced weight loss decreases the concentrations of FGF-21, chemerin, irisin, amylin, and/or PYY while it increases the concentrations of ghrelin. Fasting GIP and total bile acids circulating levels remain unaffected by diet-induced weight loss. The effect of macronutrient composition on all these molecules is not that well investigated and future research will provide more insight to this topic. Available evidence suggest that a high fat or a high protein diet increases PYY levels, a high fat or a high carbohydrate diet increases GIP levels, a high carbohydrate diet increases amylin levels while it lowers ghrelin levels as a high protein diet does. Limited evidence indicate that a high fat/low carbohydrate or a low protein diet increases FGF-21 levels while a high carbohydrate diet increases chemerin levels and a high fat diet increases bile acids levels. However, much more research is needed to confirm and expand currently available evidence. There is a great heterogeneity between the designs, sample sizes, duration and type of interventions of the existing studies and discrepancies do not allow for making firm conclusions. Furthermore, as most of the research has been performed in animals, studies on humans are of outmost important. Randomized, crossover, controlled studies with adequate sample size and duration that will examine the sole effect of weight loss after energy restriction and/or other strategies inducing weight loss as well as the effect of macronutrient composition of the diet with or without weight loss on the circulating levels of these markers will provide essential answers. Then, we will be able to design and implement better interventions for the combat against obesity, an epidemic of the modern times.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.
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