EnM
ENDOCRINOLOGY AND METABOLISM

Review Article

Endocrinol Metab 2016;31:361-372
http://dx.doi.org/10.3803/EnM.2016.31.3.361
pISSN 2093-596X · eISSN 2093-5978

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

Anna Gavrieli, Christos S. Mantzoros

Department of Endocrinology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

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

Received: 11 June 2016, **Revised**: 29 June 2016, **Accepted:** 7 July 2016
Corresponding author: Christos S. Mantzoros
Department of Endocrinology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA
Tel: +1-617-667-8630, **Fax:** +1-617-667-8634,
E-mail: cmantzor@bidmc.harvard.edu

Copyright © 2016 Korean Endocrine Society
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

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

Copyright © 2016 Korean Endocrine Society

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

Copyright © 2016 Korean Endocrine Society

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 is 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.

Copyright © 2016 Korean Endocrine Society

ORCID

Christos S. Mantzoros *http://orcid.org/0000-0003-3755-8158*

REFERENCES

1. Nishimura T, Nakatake Y, Konishi M, Itoh N. Identification of a novel FGF, FGF-21, preferentially expressed in the liver. Biochim Biophys Acta 2000;1492:203-6.
2. Kharitonenkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, et al. FGF-21 as a novel metabolic regulator. J Clin Invest 2005;115:1627-35.
3. Stein S, Stepan H, Kratzsch J, Verlohren M, Verlohren HJ, Drynda K, et al. Serum fibroblast growth factor 21 levels in gestational diabetes mellitus in relation to insulin resistance and dyslipidemia. Metabolism 2010;59:33-7.
4. Mai K, Schwarz F, Bobbert T, Andres J, Assmann A, Pfeiffer AF, et al. Relation between fibroblast growth factor-21, adiposity, metabolism, and weight reduction. Metabolism 2011;60:306-11.
5. Liu J, Xu Y, Hu Y, Wang G. The role of fibroblast growth factor 21 in the pathogenesis of non-alcoholic fatty liver disease and implications for therapy. Metabolism 2015;64: 380-90.
6. Lee J, Hong SW, Park SE, Rhee EJ, Park CY, Oh KW, et al. Exendin-4 regulates lipid metabolism and fibroblast growth factor 21 in hepatic steatosis. Metabolism 2014;63: 1041-8.
7. Hondares E, Gallego-Escuredo JM, Flachs P, Frontini A, Cereijo R, Goday A, et al. Fibroblast growth factor-21 is expressed in neonatal and pheochromocytoma-induced adult human brown adipose tissue. Metabolism 2014;63: 312-7.
8. Badman MK, Koester A, Flier JS, Kharitonenkov A, Maratos-Flier E. Fibroblast growth factor 21-deficient mice demonstrate impaired adaptation to ketosis. Endocrinology 2009;150:4931-40.
9. Zhang X, Yeung DC, Karpisek M, Stejskal D, Zhou ZG, Liu F, et al. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes 2008;57:1246-53.
10. Fisher FM, Chui PC, Antonellis PJ, Bina HA, Kharitonenkov A, Flier JS, et al. Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. Diabetes 2010;59:2781-9.
11. Buvga M, Evzen M, Pavel K, Tomas K, Vladislava Z, Pavel Z, et al. Effects of the intragastric balloon MedSil on weight loss, fat tissue, lipid metabolism, and hormones involved in energy balance. Obes Surg 2014;24:909-15.
12. Haluzikova D, Lacinova Z, Kavalkova P, Drapalova J, Krizova J, Bartlova M, et al. Laparoscopic sleeve gastrectomy differentially affects serum concentrations of FGF-19 and FGF-21 in morbidly obese subjects. Obesity (Silver Spring) 2013;21:1335-42.
13. Lips MA, de Groot GH, Berends FJ, Wiezer R, van Wagensveld BA, Swank DJ, et al. Calorie restriction and Roux-en-Y gastric bypass have opposing effects on circulating FGF21 in morbidly obese subjects. Clin Endocrinol (Oxf) 2014;81:862-70.
14. Owen BM, Ding X, Morgan DA, Coate KC, Bookout AL, Rahmouni K, et al. FGF21 acts centrally to induce sympathetic nerve activity, energy expenditure, and weight loss. Cell Metab 2014;20:670-7.
15. Bielohuby M, Menhofer D, Kirchner H, Stoehr BJ, Muller TD, Stock P, et al. Induction of ketosis in rats fed low-carbohydrate, high-fat diets depends on the relative abundance of dietary fat and protein. Am J Physiol Endocrinol Metab 2011;300:E65-76.
16. Douris N, Melman T, Pecherer JM, Pissios P, Flier JS, Cantley LC, et al. Adaptive changes in amino acid metabolism permit normal longevity in mice consuming a low-carbohydrate ketogenic diet. Biochim Biophys Acta 2015; 1852(10 Pt A):2056-65.
17. Laeger T, Henagan TM, Albarado DC, Redman LM, Bray GA, Noland RC, et al. FGF21 is an endocrine signal of protein restriction. J Clin Invest 2014;124:3913-22.
18. Muller TD, Tschop MH. Play down protein to play up metabolism? J Clin Invest 2014;124:3691-3.
19. Garcia-Caraballo SC, Comhair TM, Verheyen F, Gaemers I, Schaap FG, Houten SM, et al. Prevention and reversal of hepatic steatosis with a high-protein diet in mice. Biochim Biophys Acta 2013;1832:685-95.
20. Dushay J, Chui PC, Gopalakrishnan GS, Varela-Rey M, Crawley M, Fisher FM, et al. Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. Gastroenterology 2010;139:456-63.
21. Chu AY, Workalemahu T, Paynter NP, Rose LM, Giulianini F, Tanaka T, et al. Novel locus including FGF21 is associated with dietary macronutrient intake. Hum Mol Genet 2013;22:1895-902.
22. Tanaka T, Ngwa JS, van Rooij FJ, Zillikens MC, Wojczynski MK, Frazier-Wood AC, et al. Genome-wide meta-analysis of observational studies shows common genetic variants associated with macronutrient intake. Am J Clin

Copyright © 2016 Korean Endocrine Society

Nutr 2013;97:1395-402.
23. Wittamer V, Franssen JD, Vulcano M, Mirjolet JF, Le Poul E, Migeotte I, et al. Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids. J Exp Med 2003;198:977-85.
24. Bozaoglu K, Bolton K, McMillan J, Zimmet P, Jowett J, Collier G, et al. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology 2007;148:4687-94.
25. Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, Parlee SD, et al. Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. J Biol Chem 2007;282:28175-88.
26. Sell H, Laurencikiene J, Taube A, Eckardt K, Cramer A, Horrighs A, et al. Chemerin is a novel adipocyte-derived factor inducing insulin resistance in primary human skeletal muscle cells. Diabetes 2009;58:2731-40.
27. Mussig K, Staiger H, Machicao F, Thamer C, Machann J, Schick F, et al. RARRES2, encoding the novel adipokine chemerin, is a genetic determinant of disproportionate regional body fat distribution: a comparative magnetic resonance imaging study. Metabolism 2009;58:519-24.
28. Polyzos SA, Kountouras J, Mantzoros CS. Adipokines in nonalcoholic fatty liver disease. Metabolism 2016;65:1062-79.
29. Bao W, Baecker A, Song Y, Kiely M, Liu S, Zhang C. Adipokine levels during the first or early second trimester of pregnancy and subsequent risk of gestational diabetes mellitus: a systematic review. Metabolism 2015;64:756-64.
30. Aronis KN, Sahin-Efe A, Chamberland JP, Spiro A 3rd, Vokonas P, Mantzoros CS. Chemerin levels as predictor of acute coronary events: a case-control study nested within the veterans affairs normative aging study. Metabolism 2014;63:760-6.
31. Lehrke M, Becker A, Greif M, Stark R, Laubender RP, von Ziegler F, et al. Chemerin is associated with markers of inflammation and components of the metabolic syndrome but does not predict coronary atherosclerosis. Eur J Endocrinol 2009;161:339-44.
32. Tonjes A, Fasshauer M, Kratzsch J, Stumvoll M, Bluher M. Adipokine pattern in subjects with impaired fasting glucose and impaired glucose tolerance in comparison to normal glucose tolerance and diabetes. PLoS One 2010;5:e13911.
33. Sell H, Divoux A, Poitou C, Basdevant A, Bouillot JL, Bedossa P, et al. Chemerin correlates with markers for fatty liver in morbidly obese patients and strongly decreases after weight loss induced by bariatric surgery. J Clin Endocrinol Metab 2010;95:2892-6.
34. Ress C, Tschoner A, Engl J, Klaus A, Tilg H, Ebenbichler CF, et al. Effect of bariatric surgery on circulating chemerin levels. Eur J Clin Invest 2010;40:277-80.
35. Lee MK, Chu SH, Lee DC, An KY, Park JH, Kim DI, et al. The association between chemerin and homeostasis assessment of insulin resistance at baseline and after weight reduction via lifestyle modifications in young obese adults. Clin Chim Acta 2013;421:109-15.
36. Terra X, Auguet T, Guiu-Jurado E, Berlanga A, Orellana-Gavalda JM, Hernandez M, et al. Long-term changes in leptin, chemerin and ghrelin levels following different bariatric surgery procedures: Roux-en-Y gastric bypass and sleeve gastrectomy. Obes Surg 2013;23:1790-8.
37. Chakaroun R, Raschpichler M, Kloting N, Oberbach A, Flehmig G, Kern M, et al. Effects of weight loss and exercise on chemerin serum concentrations and adipose tissue expression in human obesity. Metabolism 2012;61:706-14.
38. Chamberland JP, Berman RL, Aronis KN, Mantzoros CS. Chemerin is expressed mainly in pancreas and liver, is regulated by energy deprivation, and lacks day/night variation in humans. Eur J Endocrinol 2013;169:453-62.
39. Kim SH, Lee SH, Ahn KY, Lee DH, Suh YJ, Cho SG, et al. Effect of lifestyle modification on serum chemerin concentration and its association with insulin sensitivity in overweight and obese adults with type 2 diabetes. Clin Endocrinol (Oxf) 2014;80:825-33.
40. Parlee SD, Wang Y, Poirier P, Lapointe M, Martin J, Bastien M, et al. Biliopancreatic diversion with duodenal switch modifies plasma chemerin in early and late post-operative periods. Obesity (Silver Spring) 2015;23:1201-8.
41. Bluher M, Rudich A, Kloting N, Golan R, Henkin Y, Rubin E, et al. Two patterns of adipokine and other biomarker dynamics in a long-term weight loss intervention. Diabetes Care 2012;35:342-9.
42. Khoo J, Dhamodaran S, Chen DD, Yap SY, Chen RY, Tian RH. Exercise-induced weight loss is more effective than dieting for improving adipokine profile, insulin resistance, and inflammation in obese men. Int J Sport Nutr Exerc Metab 2015;25:566-75.
43. Tabesh M, Hosseinzadeh MJ, Tabesh M, Esmaillzadeh A. Effects of dietary energy density on serum adipocytokine levels in diabetic women. Horm Metab Res 2013;45:834-9.
44. Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. A PGC1-α-dependent myokine that drives brown-fat-

Copyright © 2016 Korean Endocrine Society

like development of white fat and thermogenesis. Nature 2012;481:463-8.
45. Brondani LA, Boelter G, Assmann TS, Leitao CB, Canani LH, Crispim D. Irisin-encoding gene (FNDC5) variant is associated with changes in blood pressure and lipid profile in type 2 diabetic women but not in men. Metabolism 2015; 64:952-7.
46. Huh JY, Mantzoros CS. Irisin physiology, oxidative stress, and thyroid dysfunction: what next? Metabolism 2015;64: 765-7.
47. Huh JY, Mougios V, Skraparlis A, Kabasakalis A, Mantzoros CS. Irisin in response to acute and chronic whole-body vibration exercise in humans. Metabolism 2014;63:918-21.
48. Moon HS, Mantzoros CS. Regulation of cell proliferation and malignant potential by irisin in endometrial, colon, thyroid and esophageal cancer cell lines. Metabolism 2014;63: 188-93.
49. Panagiotou G, Mu L, Na B, Mukamal KJ, Mantzoros CS. Circulating irisin, omentin-1, and lipoprotein subparticles in adults at higher cardiovascular risk. Metabolism 2014;63: 1265-71.
50. Polyzos SA, Mantzoros CS. An update on the validity of irisin assays and the link between irisin and hepatic metabolism. Metabolism 2015;64:937-42.
51. Tsuchiya Y, Ando D, Takamatsu K, Goto K. Resistance exercise induces a greater irisin response than endurance exercise. Metabolism 2015;64:1042-50.
52. Polyzos SA, Mathew H, Mantzoros CS. Irisin: a true, circulating hormone. Metabolism 2015;64:1611-8.
53. Joung KE, Park KH, Filippaios A, Dincer F, Christou H, Mantzoros CS. Cord blood irisin levels are positively correlated with birth weight in newborn infants. Metabolism 2015;64:1507-14.
54. Baka S, Malamitsi-Puchner A, Boutsikou T, Boutsikou M, Marmarinos A, Hassiakos D, et al. Cord blood irisin at the extremes of fetal growth. Metabolism 2015;64:1515-20.
55. Polyzos SA, Kountouras J, Anastasilakis AD, Geladari EV, Mantzoros CS. Irisin in patients with nonalcoholic fatty liver disease. Metabolism 2014;63:207-17.
56. Bostrom PA, Fernandez-Real JM, Mantzoros C. Irisin in humans: recent advances and questions for future research. Metabolism 2014;63:178-80.
57. Crujeiras AB, Zulet MA, Lopez-Legarrea P, de la Iglesia R, Pardo M, Carreira MC, et al. Association between circulating irisin levels and the promotion of insulin resistance during the weight maintenance period after a dietary weight-lowering program in obese patients. Metabolism 2014;63:520-31.
58. Samy DM, Ismail CA, Nassra RA. Circulating irisin concentrations in rat models of thyroid dysfunction: effect of exercise. Metabolism 2015;64:804-13.
59. Crujeiras AB, Pardo M, Casanueva FF. Irisin: 'fat' or artefact. Clin Endocrinol (Oxf) 2015;82:467-74.
60. Raschke S, Eckel J. Adipo-myokines: two sides of the same coin: mediators of inflammation and mediators of exercise. Mediators Inflamm 2013;2013:320724.
61. Elsen M, Raschke S, Eckel J. Browning of white fat: does irisin play a role in humans? J Endocrinol 2014;222:R25-38.
62. Hofmann T, Elbelt U, Stengel A. Irisin as a muscle-derived hormone stimulating thermogenesis: a critical update. Peptides 2014;54:89-100.
63. Lopez-Legarrea P, de la Iglesia R, Crujeiras AB, Pardo M, Casanueva FF, Zulet MA, et al. Higher baseline irisin concentrations are associated with greater reductions in glycemia and insulinemia after weight loss in obese subjects. Nutr Diabetes 2014;4:e110.
64. Huh JY, Panagiotou G, Mougios V, Brinkoetter M, Vamvini MT, Schneider BE, et al. FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. Metabolism 2012; 61:1725-38.
65. Moreno-Navarrete JM, Ortega F, Serrano M, Guerra E, Pardo G, Tinahones F, et al. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. J Clin Endocrinol Metab 2013;98: E769-78.
66. Huh JY, Siopi A, Mougios V, Park KH, Mantzoros CS. Irisin in response to exercise in humans with and without metabolic syndrome. J Clin Endocrinol Metab 2015;100: E453-7.
67. Pardo M, Crujeiras AB, Amil M, Aguera Z, Jimenez-Murcia S, Banos R, et al. Association of irisin with fat mass, resting energy expenditure, and daily activity in conditions of extreme body mass index. Int J Endocrinol 2014;2014: 857270.
68. Swick AG, Orena S, O'Connor A. Irisin levels correlate with energy expenditure in a subgroup of humans with energy expenditure greater than predicted by fat free mass. Metabolism 2013;62:1070-3.

Copyright © 2016 Korean Endocrine Society

69. Crujeiras AB, Pardo M, Arturo RR, Navas-Carretero S, Zulet MA, Martinez JA, et al. Longitudinal variation of circulating irisin after an energy restriction-induced weight loss and following weight regain in obese men and women. Am J Hum Biol 2014;26:198-207.
70. Stengel A, Hofmann T, Goebel-Stengel M, Elbelt U, Kobelt P, Klapp BF. Circulating levels of irisin in patients with anorexia nervosa and different stages of obesity: correlation with body mass index. Peptides 2013;39:125-30.
71. Zhang Y, Li R, Meng Y, Li S, Donelan W, Zhao Y, et al. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. Diabetes 2014;63:514-25.
72. de la Iglesia R, Lopez-Legarrea P, Crujeiras AB, Pardo M, Casanueva FF, Zulet MA, et al. Plasma irisin depletion under energy restriction is associated with improvements in lipid profile in metabolic syndrome patients. Clin Endocrinol (Oxf) 2014;81:306-11.
73. Crujeiras AB, Zulet MA, Abete I, Amil M, Carreira MC, Martinez JA, et al. Interplay of atherogenic factors, protein intake and betatrophin levels in obese-metabolic syndrome patients treated with hypocaloric diets. Int J Obes (Lond) 2016;40:403-10.
74. Quinones M, Folgueira C, Sanchez-Rebordelo E, Al-Massadi O. Circulating irisin levels are not regulated by nutritional status, obesity, or leptin levels in rodents. Mediators Inflamm 2015;2015:620919.
75. Ko BJ, Park KH, Shin S, Zaichenko L, Davis CR, Crowell JA, et al. Diet quality and diet patterns in relation to circulating cardiometabolic biomarkers. Clin Nutr 2016;35:484-90.
76. Anastasilakis AD, Polyzos SA, Saridakis ZG, Kynigopoulos G, Skouvaklidou EC, Molyvas D, et al. Circulating irisin in healthy, young individuals: day-night rhythm, effects of food intake and exercise, and associations with gender, physical activity, diet, and body composition. J Clin Endocrinol Metab 2014;99:3247-55.
77. Park KH, Zaichenko L, Peter P, Davis CR, Crowell JA, Mantzoros CS. Diet quality is associated with circulating C-reactive protein but not irisin levels in humans. Metabolism 2014;63:233-41.
78. Huerta AE, Prieto-Hontoria PL, Fernandez-Galilea M, Sainz N, Cuervo M, Martinez JA, et al. Circulating irisin and glucose metabolism in overweight/obese women: effects of α-lipoic acid and eicosapentaenoic acid. J Physiol Biochem 2015;71:547-58.
79. Kawano Y, Kypta R. Secreted antagonists of the Wnt signalling pathway. J Cell Sci 2003;116(Pt 13):2627-34.
80. Ehrlund A, Mejhert N, Lorente-Cebrian S, Astrom G, Dahlman I, Laurencikiene J, et al. Characterization of the Wnt inhibitors secreted frizzled-related proteins (SFRPs) in human adipose tissue. J Clin Endocrinol Metab 2013;98:E503-8.
81. Mastaitis J, Eckersdorff M, Min S, Xin Y, Cavino K, Aglione J, et al. Loss of SFRP4 alters body size, food intake, and energy expenditure in diet-induced obese male mice. Endocrinology 2015;156:4502-10.
82. Watanabe M, Houten SM, Mataki C, Christoffolete MA, Kim BW, Sato H, et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. Nature 2006;439:484-9.
83. Ryan KK, Tremaroli V, Clemmensen C, Kovatcheva-Datchary P, Myronovych A, Karns R, et al. FXR is a molecular target for the effects of vertical sleeve gastrectomy. Nature 2014;509:183-8.
84. Pournaras DJ, Glicksman C, Vincent RP, Kuganolipava S, Alaghband-Zadeh J, Mahon D, et al. The role of bile after Roux-en-Y gastric bypass in promoting weight loss and improving glycaemic control. Endocrinology 2012;153:3613-9.
85. Gao F, Zhang X, Zhou L, Zhou S, Zheng Y, Yu J, et al. Type 2 diabetes mitigation in the diabetic Goto-Kakizaki rat by elevated bile acids following a common-bile-duct surgery. Metabolism 2016;65:78-88.
86. Prinz P, Hofmann T, Ahnis A, Elbelt U, Goebel-Stengel M, Klapp BF, et al. Plasma bile acids show a positive correlation with body mass index and are negatively associated with cognitive restraint of eating in obese patients. Front Neurosci 2015;9:199.
87. Albaugh VL, Flynn CR, Cai S, Xiao Y, Tamboli RA, Abumrad NN. Early increases in bile acids post Roux-en-Y gastric bypass are driven by insulin-sensitizing, secondary bile acids. J Clin Endocrinol Metab 2015;100:E1225-33.
88. Jahansouz C, Xu H, Hertzel AV, Serrot FJ, Kvalheim N, Cole A, et al. Bile acids increase independently from hypocaloric restriction after bariatric surgery. Ann Surg 2015 Dec 10 [Epub]. http://dx.doi.org/10.1097/SLA.0000000000001552.
89. Nakatani H, Kasama K, Oshiro T, Watanabe M, Hirose H, Itoh H. Serum bile acid along with plasma incretins and serum high-molecular weight adiponectin levels are increased after bariatric surgery. Metabolism 2009;58:1400-7.
90. Patti ME, Houten SM, Bianco AC, Bernier R, Larsen PR,

Copyright © 2016 Korean Endocrine Society

Holst JJ, et al. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. Obesity (Silver Spring) 2009;17:1671-7.
91. Nyhlin H, Brydon G, Danielsson A, Eriksson F. Bile acid malabsorption after intestinal bypass surgery for obesity: a comparison between jejunoileal shunt and biliointestinal bypass. Int J Obes 1990;14:47-55.
92. Simonen M, Dali-Youcef N, Kaminska D, Venesmaa S, Kakela P, Paakkonen M, et al. Conjugated bile acids associate with altered rates of glucose and lipid oxidation after Roux-en-Y gastric bypass. Obes Surg 2012;22:1473-80.
93. Kohli R, Bradley D, Setchell KD, Eagon JC, Abumrad N, Klein S. Weight loss induced by Roux-en-Y gastric bypass but not laparoscopic adjustable gastric banding increases circulating bile acids. J Clin Endocrinol Metab 2013;98:E708-12.
94. Trouillot TE, Pace DG, McKinley C, Cockey L, Zhi J, Haeussler J, et al. Orlistat maintains biliary lipid composition and hepatobiliary function in obese subjects undergoing moderate weight loss. Am J Gastroenterol 2001;96:1888-94.
95. Kudchodkar BJ, Sodhi HS, Mason DT, Borhani NO. Effects of acute caloric restriction on cholesterol metabolism in man. Am J Clin Nutr 1977;30:1135-46.
96. Raymond F, Wang L, Moser M, Metairon S, Mansourian R, Zwahlen MC, et al. Consequences of exchanging carbohydrates for proteins in the cholesterol metabolism of mice fed a high-fat diet. PLoS One 2012;7:e49058.
97. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014;505:559-63.
98. Thorning TK, Raziani F, Bendsen NT, Astrup A, Tholstrup T, Raben A. Diets with high-fat cheese, high-fat meat, or carbohydrate on cardiovascular risk markers in overweight postmenopausal women: a randomized crossover trial. Am J Clin Nutr 2015;102:573-81.
99. Reddy BS, Engle A, Simi B, O'Brien LT, Barnard RJ, Pritikin N, et al. Effect of low-fat, high-carbohydrate, high-fiber diet on fecal bile acids and neutral sterols. Prev Med 1988; 17:432-9.
100. Martucci CP, Miller DG, Levine B, Tint GS, Fishman J. Changes in serum bile acids in normal human subjects following the adoption of a low-fat diet. Ann N Y Acad Sci 1995;768:331-3.
101. Ryter SW, Alam J, Choi AM. Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. Physiol Rev 2006;86:583-650.
102. Zheng Y, Toborek M, Hennig B. Epigallocatechin gallate-mediated protection against tumor necrosis factor-α-induced monocyte chemoattractant protein-1 expression is heme oxygenase-1 dependent. Metabolism 2010;59:1528-35.
103. Shakeri-Manesch S, Zeyda M, Huber J, Ludvik B, Prager G, Stulnig TM. Diminished upregulation of visceral adipose heme oxygenase-1 correlates with waist-to-hip ratio and insulin resistance. Int J Obes (Lond) 2009;33:1257-64.
104. Jais A, Einwallner E, Sharif O, Gossens K, Lu TT, Soyal SM, et al. Heme oxygenase-1 drives metaflammation and insulin resistance in mouse and man. Cell 2014;158:25-40.
105. Galbraith RA, Kappas A. Regulation of food intake and body weight by cobalt porphyrins in animals. Proc Natl Acad Sci U S A 1989;86:7653-7.
106. Peterson SJ, Drummond G, Kim DH, Li M, Kruger AL, Ikehara S, et al. L-4F treatment reduces adiposity, increases adiponectin levels, and improves insulin sensitivity in obese mice. J Lipid Res 2008;49:1658-69.
107. Galbraith RA, Kappas A. Intracerebroventricular administration of cobalt protoporphyrin elicits prolonged weight reduction in rats. Am J Physiol 1991;261(6 Pt 2):R1395-401.
108. Galbraith RA, Kow LM, Pfaff D, Kappas A. Injection of cobalt protoporphyrin into the medial nuclei of the hypothalamus elicits weight loss. Am J Physiol 1992;263(4 Pt 2): R805-12.
109. Hosick PA, AlAmodi AA, Storm MV, Gousset MU, Pruett BE, Gray W 3rd, et al. Chronic carbon monoxide treatment attenuates development of obesity and remodels adipocytes in mice fed a high-fat diet. Int J Obes (Lond) 2014;38:132-9.
110. Li M, Kim DH, Tsenovoy PL, Peterson SJ, Rezzani R, Rodella LF, et al. Treatment of obese diabetic mice with a heme oxygenase inducer reduces visceral and subcutaneous adiposity, increases adiponectin levels, and improves insulin sensitivity and glucose tolerance. Diabetes 2008;57:1526-35.
111. Chakrabarty A, Emerson MR, LeVine SM. Heme oxygenase-1 in SJL mice with experimental allergic encephalomyelitis. Mult Scler 2003;9:372-81.
112. Csongradi E, Docarmo JM, Dubinion JH, Vera T, Stec DE. Chronic HO-1 induction with cobalt protoporphyrin (CoPP) treatment increases oxygen consumption, activity, heat production and lowers body weight in obese melanocor-

Copyright © 2016 Korean Endocrine Society

tin-4 receptor-deficient mice. Int J Obes (Lond) 2012;36:244-53.
113. Tu TH, Joe Y, Choi HS, Chung HT, Yu R. Induction of heme oxygenase-1 with hemin reduces obesity-induced adipose tissue inflammation via adipose macrophage phenotype switching. Mediators Inflamm 2014;2014:290708.
114. Abraham NG, Sodhi K, Silvis AM, Vanella L, Favero G, Rezzani R, et al. CYP2J2 targeting to endothelial cells attenuates adiposity and vascular dysfunction in mice fed a high-fat diet by reprogramming adipocyte phenotype. Hypertension 2014;64:1352-61.
115. Cao J, Peterson SJ, Sodhi K, Vanella L, Barbagallo I, Rodella LF, et al. Heme oxygenase gene targeting to adipocytes attenuates adiposity and vascular dysfunction in mice fed a high-fat diet. Hypertension 2012;60:467-75.
116. Tuzcu M, Sahin N, Orhan C, Agca CA, Akdemir F, Tuzcu Z, et al. Impact of chromium histidinate on high fat diet induced obesity in rats. Nutr Metab (Lond) 2011;8:28.
117. Huang JY, Chiang MT, Chau LY. Adipose overexpression of heme oxygenase-1 does not protect against high fat diet-induced insulin resistance in mice. PLoS One 2013;8:e55369.
118. Wren AM, Seal LJ, Cohen MA, Brynes AE, Frost GS, Murphy KG, et al. Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab 2001;86:5992.
119. Mishra AK, Dubey V, Ghosh AR. Obesity: an overview of possible role(s) of gut hormones, lipid sensing and gut microbiota. Metabolism 2016;65:48-65.
120. Shimada T, Furuta H, Doi A, Ariyasu H, Kawashima H, Wakasaki H, et al. Des-acyl ghrelin protects microvascular endothelial cells from oxidative stress-induced apoptosis through sirtuin 1 signaling pathway. Metabolism 2014;63:469-74.
121. Wang L, Li G, Chen Q, Ke D. Octanoylated ghrelin attenuates angiogenesis induced by oxLDL in human coronary artery endothelial cells via the GHSR1a-mediated NF-κB pathway. Metabolism 2015;64:1262-71.
122. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 2001; 50:1714-9.
123. Callahan HS, Cummings DE, Pepe MS, Breen PA, Matthys CC, Weigle DS. Postprandial suppression of plasma ghrelin level is proportional to ingested caloric load but does not predict intermeal interval in humans. J Clin Endocrinol Metab 2004;89:1319-24.
124. Shiiya T, Nakazato M, Mizuta M, Date Y, Mondal MS, Tanaka M, et al. Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. J Clin Endocrinol Metab 2002;87:240-4.
125. Zwirska-Korczala K, Konturek SJ, Sodowski M, Wylezol M, Kuka D, Sowa P, et al. Basal and postprandial plasma levels of PYY, ghrelin, cholecystokinin, gastrin and insulin in women with moderate and morbid obesity and metabolic syndrome. J Physiol Pharmacol 2007;58 Suppl 1:13-35.
126. le Roux CW, Patterson M, Vincent RP, Hunt C, Ghatei MA, Bloom SR. Postprandial plasma ghrelin is suppressed proportional to meal calorie content in normal-weight but not obese subjects. J Clin Endocrinol Metab 2005;90:1068-71.
127. Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, et al. Inhibition of food intake in obese subjects by peptide YY3-36. N Engl J Med 2003;349:941-8.
128. Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med 2002;346:1623-30.
129. Hansen TK, Dall R, Hosoda H, Kojima M, Kangawa K, Christiansen JS, et al. Weight loss increases circulating levels of ghrelin in human obesity. Clin Endocrinol (Oxf) 2002;56:203-6.
130. Overduin J, Frayo RS, Grill HJ, Kaplan JM, Cummings DE. Role of the duodenum and macronutrient type in ghrelin regulation. Endocrinology 2005;146:845-50.
131. Murray CD, le Roux CW, Gouveia C, Bassett P, Ghatei MA, Bloom SR, et al. The effect of different macronutrient infusions on appetite, ghrelin and peptide YY in parenterally fed patients. Clin Nutr 2006;25:626-33.
132. Koliaki C, Kokkinos A, Tentolouris N, Katsilambros N. The effect of ingested macronutrients on postprandial ghrelin response: a critical review of existing literature data. Int J Pept 2010;2010:710852.
133. van der Klaauw AA, Keogh JM, Henning E, Trowse VM, Dhillo WS, Ghatei MA, et al. High protein intake stimulates postprandial GLP1 and PYY release. Obesity (Silver Spring) 2013;21:1602-7.
134. Gibbons C, Caudwell P, Finlayson G, Webb DL, Hellstrom PM, Naslund E, et al. Comparison of postprandial profiles of ghrelin, active GLP-1, and total PYY to meals varying in fat and carbohydrate and their association with hunger

Copyright © 2016 Korean Endocrine Society

and the phases of satiety. J Clin Endocrinol Metab 2013;98:E847-55.
135. le Roux CW, Bloom SR. Peptide YY, appetite and food intake. Proc Nutr Soc 2005;64:213-6.
136. Michalakis K, Goulis DG, Vazaiou A, Mintziori G, Polymeris A, Abrahamian-Michalakis A. Obesity in the ageing man. Metabolism 2013;62:1341-9.
137. le Roux CW, Batterham RL, Aylwin SJ, Patterson M, Borg CM, Wynne KJ, et al. Attenuated peptide YY release in obese subjects is associated with reduced satiety. Endocrinology 2006;147:3-8.
138. Sodowski K, Zwirska-Korczala K, Kuka D, Kukla M, Budziszewska P, Czuba B, et al. Basal and postprandial gut peptides affecting food intake in lean and obese pregnant women. J Physiol Pharmacol 2007;58 Suppl 1:37-52.
139. Cahill F, Ji Y, Wadden D, Amini P, Randell E, Vasdev S, et al. The association of serum total peptide YY (PYY) with obesity and body fat measures in the CODING study. PLoS One 2014;9:e95235.
140. Pfluger PT, Kampe J, Castaneda TR, Vahl T, D'Alessio DA, Kruthaupt T, et al. Effect of human body weight changes on circulating levels of peptide YY and peptide YY3-36. J Clin Endocrinol Metab 2007;92:583-8.
141. Cahill F, Shea JL, Randell E, Vasdev S, Sun G. Serum peptide YY in response to short-term overfeeding in young men. Am J Clin Nutr 2011;93:741-7.
142. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med 2011;365:1597-604.
143. Moran LJ, Noakes M, Clifton PM, Wittert GA, Le Roux CW, Ghatei MA, et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr 2007;86:1603-10.
144. McNeil J, Schwartz A, Rabasa-Lhoret R, Lavoie JM, Brochu M, Doucet E. Changes in leptin and peptide YY do not explain the greater-than-predicted decreases in resting energy expenditure after weight loss. J Clin Endocrinol Metab 2015;100:E443-52.
145. Lewis HB, Ahern AL, Solis-Trapala I, Walker CG, Reimann F, Gribble FM, et al. Effect of reducing portion size at a compulsory meal on later energy intake, gut hormones, and appetite in overweight adults. Obesity (Silver Spring) 2015;23:1362-70.
146. Batterham RL, Heffron H, Kapoor S, Chivers JE, Chandarana K, Herzog H, et al. Critical role for peptide YY in protein-mediated satiation and body-weight regulation. Cell Metab 2006;4:223-33.
147. Helou N, Obeid O, Azar ST, Hwalla N. Variation of postprandial PYY 3-36 response following ingestion of differing macronutrient meals in obese females. Ann Nutr Metab 2008;52:188-95.
148. El Khoury D, El-Rassi R, Azar S, Hwalla N. Postprandial ghrelin and PYY responses of male subjects on low carbohydrate meals to varied balancing proportions of proteins and fats. Eur J Nutr 2010;49:493-500.
149. Cooper JA. Factors affecting circulating levels of peptide YY in humans: a comprehensive review. Nutr Res Rev 2014; 27:186-97.
150. Essah PA, Levy JR, Sistrun SN, Kelly SM, Nestler JE. Effect of macronutrient composition on postprandial peptide YY levels. J Clin Endocrinol Metab 2007;92:4052-5.
151. Ludvik B, Kautzky-Willer A, Prager R, Thomaseth K, Pacini G. Amylin: history and overview. Diabet Med 1997;14 Suppl 2:S9-13.
152. Lutz TA. Pancreatic amylin as a centrally acting satiating hormone. Curr Drug Targets 2005;6:181-9.
153. Morley JE, Flood JF. Amylin decreases food intake in mice. Peptides 1991;12:865-9.
154. Rushing PA, Hagan MM, Seeley RJ, Lutz TA, Woods SC. Amylin: a novel action in the brain to reduce body weight. Endocrinology 2000;141:850-3.
155. Trevaskis JL, Lei C, Koda JE, Weyer C, Parkes DG, Roth JD. Interaction of leptin and amylin in the long-term maintenance of weight loss in diet-induced obese rats. Obesity (Silver Spring) 2010;18:21-6.
156. Mietlicki-Baase EG, Olivos DR, Jeffrey BA, Hayes MR. Cooperative interaction between leptin and amylin signaling in the ventral tegmental area for the control of food intake. Am J Physiol Endocrinol Metab 2015;308:E1116-22.
157. Reda TK, Geliebter A, Pi-Sunyer FX. Amylin, food intake, and obesity. Obes Res 2002;10:1087-91.
158. Dunn-Meynell AA, Le Foll C, Johnson MD, Lutz TA, Hayes MR, Levin BE. Endogenous VMH amylin signaling is required for full leptin signaling and protection from diet-induced obesity. Am J Physiol Regul Integr Comp Physiol 2016;310:R355-65.
159. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, et al. Ketosis and appetite-mediating nutrients and hormones after weight loss. Eur J Clin Nutr 2013;67:759-64.

Copyright © 2016 Korean Endocrine Society

160. Eller LK, Ainslie PN, Poulin MJ, Reimer RA. Differential responses of circulating amylin to high-fat vs. high-carbohydrate meal in healthy men. Clin Endocrinol (Oxf) 2008;68:890-7.
161. Sjolund K, Sanden G, Hakanson R, Sundler F. Endocrine cells in human intestine: an immunocytochemical study. Gastroenterology 1983;85:1120-30.
162. Phillips LK, Prins JB. Update on incretin hormones. Ann N Y Acad Sci 2011;1243:E55-74.
163. Geloneze B, de Oliveira Mda S, Vasques AC, Novaes FS, Pareja JC, Tambascia MA. Impaired incretin secretion and pancreatic dysfunction with older age and diabetes. Metabolism 2014;63:922-9.
164. de Mello AH, Pra M, Cardoso LC, de Bona Schraiber R, Rezin GT. Incretin-based therapies for obesity treatment. Metabolism 2015;64:967-81.
165. Flint A, Gregersen NT, Gluud LL, Moller BK, Raben A, Tetens I, et al. Associations between postprandial insulin and blood glucose responses, appetite sensations and energy intake in normal weight and overweight individuals: a meta-analysis of test meal studies. Br J Nutr 2007;98:17-25.
166. Edholm T, Degerblad M, Gryback P, Hilsted L, Holst JJ, Jacobsson H, et al. Differential incretin effects of GIP and GLP-1 on gastric emptying, appetite, and insulin-glucose homeostasis. Neurogastroenterol Motil 2010;22:1191-200.
167. Meier JJ, Goetze O, Anstipp J, Hagemann D, Holst JJ, Schmidt WE, et al. Gastric inhibitory polypeptide does not inhibit gastric emptying in humans. Am J Physiol Endocrinol Metab 2004;286:E621-5.
168. Jones IR, Owens DR, Luzio SD, Hayes TM. Obesity is associated with increased post-prandial GIP levels which are not reduced by dietary restriction and weight loss. Diabete Metab 1989;15:11-22.
169. Weiss EP, Albert SG, Reeds DN, Kress KS, Ezekiel UR, McDaniel JL, et al. Calorie restriction and matched weight loss from exercise: independent and additive effects on glucoregulation and the incretin system in overweight women and men. Diabetes Care 2015;38:1253-62.
170. Santo MA, Riccioppo D, Pajecki D, Kawamoto F, de Cleva R, Antonangelo L, et al. Weight regain after gastric bypass: influence of gut hormones. Obes Surg 2016;26:919-25.
171. Elliott RM, Morgan LM, Tredger JA, Deacon S, Wright J, Marks V. Glucagon-like peptide-1 (7-36)amide and glucose-dependent insulinotropic polypeptide secretion in response to nutrient ingestion in man: acute post-prandial and 24-h secretion patterns. J Endocrinol 1993;138:159-66.
172. Gribble FM. The gut endocrine system as a coordinator of postprandial nutrient homoeostasis. Proc Nutr Soc 2012;71:456-62.
173. Runchey SS, Valsta LM, Schwarz Y, Wang C, Song X, Lampe JW, et al. Effect of low- and high-glycemic load on circulating incretins in a randomized clinical trial. Metabolism 2013;62:188-95.

Copyright © 2016 Korean Endocrine Society