Ghrelin, Obestatin and Leptin in Childhood Obesity

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1 Introduction

The prevalence of obesity among children and adolescents is progressively increasing worldwide and has become an epidemic. Childhood obesity is associated with the early development of diseases such as type 2 diabetes and cardiovascular disease. The cytokines leptin, ghrelin and obestatin play significant roles in regulating body mass. Discovery of the Ob gene in 1994 (Zhang et al., 1994) has led to rapid advances in the understanding of obesity. The discovery of leptin, the product of Ob gene, led to understanding that leptin regulates body weight and fat deposition through effects on metabolism and appetite (Pelleymounter et al., 1995) and food intake (Halaas et al., 1995). That followed the understanding that mutations in Ob gene or in the gene encoding the OB receptor (OB-R) results in obesity. Then, the discovery of ghrelin elucidated the role of the stomach as an important organ in the regulation of growth hormone release and energy homeostasis. Improving our understanding of the biochemical mechanisms accounting for the differences in appetite hormones among individuals with varying body size and adiposity should aid in the development of future therapies to prevent and treat obesity.

Leptin is secreted primarily by adipocytes, acts within the mediobasal hypothalamus to control food intake and energy expenditure. Obestatin and ghrelin are two peptide hormones with opposing action in weight regulation that are derived from the same ghrelin gene. After differential modification, these hormones activate distinct receptors. Ghrelin promotes food intake and obesity in rodent models, while obestatin has been shown to have activities that oppose the effects of ghrelin: It suppresses food intake, delays gastric emptying, and decreases weight gain in rodents. Recent research has provided information on their genetics, normal circulating levels, and relationship to insulin levels, which may offer possibilities for treatment of childhood obesity.

2 Childhood Obesity

Childhood obesity is becoming a global epidemic. In the National Health and Nutrition Examination Survey (NHANES) survey performed in 2003-2004, the proportion of adolescents who were overweight (defined as at or above the 95th percentile of the sex-specific BMI for age growth charts) reached 17.1%. In adults, the prevalence of obesity (BMI ≥ 30) was 32.2%, and the prevalence of extreme obesity (BMI ≥ 40) was 6.9% in women and 2.8% in men. Today, in the USA the populations with the highest frequency of children and adolescents who are overweight or obese are the Mexican-American and non-Hispanic black. Twin studies suggest a heritability of fat mass, and disorders of energy balance that arise from genetic defects have been identified. Early childhood obesity is considered to be the dominant predictor of obesity 5 years later (Salbe et al., 2002). Critical periods of development are said to exist for the development of obesity and its complications. These include gestation and early infancy, the period of adiposity rebound that occurs between 5 and 7 yrs. of age, and adolescence (Dietz, 1994). In the future, as leptin, ghrelin, and obestatin are better understood, they may play a role in managing childhood obesity.
3  Leptin

Leptin, the product of the ob gene identified in 1994, is a 167-amino acid (16 KDa) containing gene product. It is a hormone secreted predominantly by adipocytes. Other tissues that express leptin, though in small amounts, include placenta, ovaries, skeletal muscle, stomach, pituitary, and liver. Leptin demonstrates structural similarities with the cytokine family. Leptin acts within the mediobasal hypothalamus to control food intake and energy expenditure. Its discovery ushered in a decade of research that went on to describe not only the specific nuclei and cell type, such as proopio-melanocortin neurons of the arcuate nucleus, that respond to leptin but also the signaling cascades that mediated its effects.

3.1  Genetics

The human leptin gene is located on chromosome 7q31.3. It has three exons and two introns. Its promoter region has sites such as a TATA box and CCAAT/enhancer binding protein (C/EBP), glucocorticoid response element (GRE) and AMPc response element (CRE). Leptin acts through the leptin receptor.

3.2  Leptin Receptor

The leptin receptor gene is located on chromosome 1p31 and is highly expressed in the hypothalamus and cerebellum. The leptin receptor is a large single membrane spanning protein and belongs to the gp 130 family of cytokine class 1 receptors, located throughout the central nervous system and peripheral tissues. There are at least six receptor isoforms with different C-terminal cytoplasmic domains identified. They are ObRa, ObRb, ObRc, ObRd, ObRe, and ObRf (Bluher & Mantzoros, 2009). All these isoforms differ at the intracellular carboxy terminals, but have identical extracellular ligand binding domains. OB-R isoforms are divided into three classes: long, short, and soluble isoforms. The long isoform OB-Rb is expressed throughout the central nervous system and is considered to be the major signaling isoform since it is the only isoform that can transmit the leptin signal via the complete JAK-STAT pathway (janus kinase 2 and the activators of transcription STAT 3,5 and 6). OB-Rb is expressed throughout the body and has been located in the hypothalamus, monocytes, lymphocytes, pancreatic beta cells, enterocytes, endothelial, smooth muscle, and other cell types. The ObRb receptor is particularly important in the hypothalamus, where it regulates energy homeostasis and neuroendocrine function. The soluble leptin receptor isoform ObRe is the extracellular cleaved part of the long isoform ObRb and the main circulating leptin-binding protein. The short isoforms ObRa and ObRc are thought to have important roles in transporting leptin across the blood-brain barrier (Bluher & Mantzoros, 2009; Mantzoros et al., 2011).

3.3  Metabolic and Endocrinal Factors That Contribute to Regulating Transcription

Leptin concentrations rise with increasing fat mass; individuals with low fat mass, such as those with lipodystrophy syndromes and anorexia nervosa, have low circulating leptin concentrations (Oral et al., 2002; Havel et al., 1996; Considine et al., 1996; Maffei et al., 1995). Insulin exhibits a directly proportional relationship with leptin levels. Glucocorticoids, estrogens, inflammatory cytokines and acute infectious states increase them, while low temperatures, adrenergic stimulation, growth hormone (GH), thyroid hormones, androgens, melatonin and smoking appear to reduce levels. The levels also exhibit circadian oscillation, with higher plasma concentrations at night.
3.4 Circulating Leptin Levels

In humans, leptin is released in pulsatile fashion and follows a circadian rhythm with highest levels between midnight and early morning and lowest levels in the early to mid-afternoon (Scheer et al., 2009; Sinha et al., 1996). The obese have higher pulse amplitudes (Sinha et al., 1996). The level of Ob mRNA in white adipose tissue and the circulating leptin are closely associated with the amount of fat mass. Women have higher levels of leptin compared to age and body mass index (BMI) matched men (Mantzoros & Moschos, 1998). Serum leptin levels are significantly higher in females compared to males, after correcting for total body fat. Higher leptin levels in females indicate leptin resistance and play an important role in the regulation of reproductive function (Dubey et al., 2007).

Plasma leptin levels come down with fasting or dieting and rapidly recover during fed state. Leptin expression is said to be increased by insulin, glucose, estrogens, glucocorticoids, TNF alpha, interleukin-1 as well as by conditions of impaired renal function and acute inflammation. Leptin levels are said to decrease in response to beta-adrenoreceptor agonists, androgens, cold exposure, thiazolidinediones, and cigarette smoking. Besides the above-mentioned neuroendocrine effects of leptin on the control of food intake and energy expenditure, Ob receptors have been proven in lung, intestine, kidney, liver, skin, stomach, heart, spleen, as well as in other organs, suggesting the implication of leptin in directly regulating immune cells, pancreatic beta cells, adipocytes, muscle, and blood cells.

3.5 Leptin Levels in Pathological Status

3.5.1 Leptin Deficiency

Leptin has emerged over the past decade as a key hormone in not only the regulation of food intake and energy expenditure but also in the regulation of neuroendocrine and immune function as well as the modulation of glucose and fat metabolism as shown by numerous observational and interventional studies in humans with (complete) congenital or relative leptin deficiency. Leptin deficiency is an uncommon cause of obesity. The relatively acute effects on circulating thyroid hormone concentrations provide compelling evidence in humans that leptin is a regulator of the hypothalamic-pituitary-thyroidal axis (Farooqi et al., 2002; Rosenbaum et al., 2002). In addition, the immunodeficient state associated with human leptin deficiency was reversed by leptin therapy (Faroqi et al., 2002). Congenital leptin deficiency is a rare cause of early onset obesity. To date, only four families with disrupting leptin gene mutations have been identified and three of them are of Pakistani origin. Four of the affected children were subjected to recombinant leptin therapy. In all cases, this resulted in a dramatic reversal of the phenotype of hyperphagia accompanied by hyperinsulinemia, hyperlipidemia, and other metabolic, neuroendocrine, and immune dysfunctions. Leptin treatment of three leptin deficient adults led to an average weight loss of 18 kg, accompanied by a 58% reduction in energy intake and an increase of 62% in 24-hour fat oxidation in these patients. DNA polymorphisms in the OB gene may be linked to obesity.

3.5.2 Leptin Resistance

It was postulated that the presence of chronically high leptin concentrations in overweight individuals was a result of resistance to the effects of leptin in these individuals (Considine et al., 1996) even though relatively few were found to have function-altering genetic defects of the leptin receptor itself (Echwald et al., 1997). High serum leptin, independent of body fat, may be an indicator of increased leptin resistance, which predisposes children at high risk for adult obesity to somewhat greater growth in weight and body fat during childhood (Fleisch et al., 2007). Changes in weight status in infancy may influence
risk of later obesity more than weight status at birth. More-rapid increases in weight for length in the first 6 months of life were associated with sharply increased risk of obesity at 3 years of age (Taveras et al., 2009). Lower cord blood leptin levels are said to be associated with smaller size at birth but more pronounced weight gain in the first 6 months of life and higher BMI at 3 years of age (Mantzoros et al., 2008). In a recent study, it was noted that higher neonatal leptin and gestational diabetes predicted slower weight gain in the first 6 months of life (Parker et al., 2010).

Inactivating mutations affecting both alleles of the leptin gene result in excessive food intake and severe, early-onset obesity in the context of very low (< 5 ng/mL) serum leptin concentrations. These features are successfully reversed with leptin therapy. Leptin receptor mutations were first described in the context of markedly supraphysiologic serum leptin; however, more recent studies suggest substantial overlap in serum leptin among those with and without function-altering leptin receptor mutations. Leptin concentrations have thus not been successfully used to identify those bearing leptin receptor abnormalities.

3.5.3 Human Congenital Leptin Deficiency

Human congenital leptin deficiency is a rare autosomal recessive disease caused by mutations in the leptin gene. Subjects with leptin deficiency due to a missense leptin gene mutation have severe obesity and hyperphagia. Congenital leptin deficiency is associated with hypogonadotropic hypogonadism and manifests with absence of growth spurt, lack of secondary sex characteristics and failure to reach puberty (Ozata et al., 1999; Strobel et al., 1998). Subjects with congenital leptin deficiency have a higher incidence of infections with higher mortality. The odds ratio for mortality in the context of this obesity phenotype is 25.4, indicating that this mutation severely impairs key biological functions during childhood, negatively impacting on survival (Ozata et al., 1999). Leptin replacement leads to marked weight loss and improves insulin resistance and dyslipidemia and results in appropriate progression through puberty (Farooqi et al., 2002). Though patients with congenital leptin deficiency have age- and sex-appropriate BMC and BMD, leptin treatment increases their skeletal maturation (Farooqi et al., 2002). Leptin is currently available for life-long treatment of subjects with congenital leptin deficiency through an Amylin-pharmaceutical company sponsored compassionate leptin access program.

3.6 Congenital Lipoatrophy

Congenital generalized lipodystrophy (CGL) or lipoatrophy is an autosomal recessive disease. It is characterized by the absence of or scant adipose tissue, the development of severe insulin resistance early in life, hypertriglyceridemia, hepatomegaly, and the development of diabetes mellitus during puberty (Nishiyama et al., 2009). Two genes were identified as causative genes for CGL. It is caused by mutations in gene encoding BSCL2 and 1-acylglycerol-3-phosphate O-acyltransferase-2 (AGPAT2) (Haghighi et al., 2012). Therapy with leptin proved to be effective and safe for therapy-resistant diabetes and hypertriglyceridemia in patients with congenital lipodystrophy (Jazet et al., 2013).

3.6.1 Leptin Therapy in Lipodystrophy

In contrast to findings in leptin deficient lipodystrophic subjects, with high concentrations of not only insulin but also leptin presumably due to leptin tolerance or resistance (Mantzoros, 2012; Mantzoros et al., 1998), treatment with additional exogenous leptin has not been associated with significant weight loss or reduction in metabolic complications (Mantzoros, 2012).
4 Ghrelin

Ghrelin was identified in 1999 as the endogenous ligand for the growth hormone secretagogue receptor 1a (GHSR 1a) (Kojima et al., 1999). Ghrelin is an acyl-peptide hormone, composed of 28 amino acids, in which serine 3 (threonine 3 in frogs) is modified by an n-octanoic acid; this modification is essential for ghrelin to bind with its receptor, the growth hormone secretagogue receptor (GHS-R) (Kojima et al., 2009).

4.1 Circulating Ghrelin Levels

Ghrelin is secreted principally by the gastric fundus and proximal small intestine. Ghrelin circulates in the blood stream under fasting conditions, indicating that it transmits a hunger signal from the periphery to the central nervous system. It is also found in the hypothalamus, pituitary gland, hippocampus, brain cortex, adrenal gland, intestine, pancreas, and many other human tissues (Kojima et al., 2009; Gnanapavan et al., 2002). Regulation of ghrelin concentration may occur at different levels ranging from transcription, posttranscription, translation, post-translation modification to secretion, suggesting the remarkable complexity of its regulation. It promotes a positive energy balance, and its action is mediated predominantly by central nervous system pathways controlling food intake, energy expenditure, and nutrient partitioning. Ghrelin levels respond in a different manner to glucose, lipid and protein loads, and are subject to modulation according to gender, obesity and insulin sensitivity (Greenman et al., 2004).

4.2 Metabolic and Endocrinal Factors That Contribute to Regulating Transcription

Many reports show that ghrelin level is negatively correlated with body mass index in humans in physiological and many pathological statuses (Greenman et al., 2004; Purnell et al., 2003). Fasting ghrelin levels were negatively related to body mass index, waist circumference, waist/hip ratio, fasting insulin and homeostasis model assessment insulin resistance index (HOMA-R) (Greenman et al., 2004). Insulin may negatively regulate ghrelin and high-density lipoprotein may be a carrier particle for circulating ghrelin (Purnell et al., 2003). Total ghrelin level is inversely associated with fat cell volume (Purnell et al., 2003) and specifically in women, with total fat mass and fat mass/lean mass ratio, whereas in men it is associated with abdominal fat mass and fat distribution index (Makovey et al., 2007). In women, plasma ghrelin correlated inversely with body mass index (BMI, \( r = -0.32 \)), total fat mass \( (r = -0.30) \) and fat mass/lean mass ratio \( (r = -0.42) \), whereas in men associations with abdominal fat mass \( (r = -0.31) \) and fat distribution index \( (r = -0.33) \) were observed (Makovey et al., 2007).

4.3 Ghrelin Levels in Pathological Status

Ghrelin levels alter in several disease states; the discussion follows (Jazet et al., 2013).

4.3.1 Prader-Willi Syndrome

Prader-Willi Syndrome (PWS) is a genetic disorder due to the loss of expression of paternally inherited genes encoded on the proximal long arm of chromosome 15 (15q11.2–q13), leading to life-threatening insatiable hunger and obesity from early childhood, developmental abnormalities of the brain, particularly hypothalamic defects. Changes in orexigenic NPY and AGRP hypothalamic neurons, or anorexigenic oxytocin neurons have been found in illness and PWS. PWS subjects have inappropriately elevated plasma ghrelin for their obesity, at least partly explained by preserved insulin sensitivity (Goldstone,
In a study of Ghrelin levels in young children with PWS, Erdie-Lalena et al. (2006) found that children < 5 years of age with PWS, who had not yet developed hyperphagia or excessive obesity, had normal ghrelin levels, in contrast to the hyperghrelinemia of older, hyperphagic people with PWS. They postulated that it is possible that ghrelin levels increase suddenly before hyperphagia develops. Early diagnosis and understanding of molecular mechanisms (Bittel & Butler, 2005) of PWS is important for effective long-term management that includes a multidisciplinary approach to improve quality of life, prevent complications, and prolong life expectancy (Elena et al., 2012).

4.3.2 Anorexia Nervosa

Ghrelin levels were increased in anorexia nervosa as well as illness-induced cachexia and it was considered that increased ghrelin may represent a compensatory mechanism under catabolic-anabolic imbalance in cachectic patients (Nagaya et al., 2001). Low ghrelin is independently (positively) associated with metabolic syndrome, type 2 diabetes, insulin concentration, and insulin resistance (Poykko et al., 2003). There is a negative correlation between ghrelin and body weight. The growth hormone secretagogue receptor (GHSR) (ghrelin receptor) plays an important role in the regulation of food intake and energy homeostasis. Common polymorphisms in GHSR have been associated with obesity in both a cross-sectional and a family-based association study (Baessler et al., 2004). In a study of common genetic variation in GHSR for association with body size in children and adults, common variation in GHSR was not found to be associated with body size in U.K. adults or children (Garcia et al., 2008).

4.4 Ghrelin in Growth and Development

Ghrelin is present in the fetus and its tissue distribution differs from the adult. It binds to the GHS-R as early as during the fetal period. Ghrelin is present in the perinatal period in humans where its role remains poorly understood. In adolescents, similar to adults, plasma ghrelin concentrations are decreased and increased in the presence of a positive and a negative energy balance, respectively. In animal studies, serum ghrelin concentrations were increased by fasting and reduced by re-feeding or oral glucose administration, but not by water ingestion, indicating that in addition to its role in regulating GH secretion, ghrelin signals the hypothalamus when an increase in metabolic efficiency is necessary (Tschop et al., 2000). Whether these changes represent an adaptive response aiming at optimizing fat utilization as suggested in animal studies (Tschop et al., 2000; Wortley et al., 2004) or whether they reflect an altered set-point for ghrelin at the hypothalamic level is presently unknown.

4.5 Ghrelin and Insulin Resistance

Evidence suggests that glucose and insulin metabolism may be implicated in the regulation of ghrelin levels. Plasma ghrelin concentrations in patients with simple obesity and anorexia nervosa were lower and higher, respectively, than those of healthy subjects with normal body weight. Plasma ghrelin concentrations of normal subjects decreased significantly after oral and intra venous glucose administration; a similar response was also observed in diabetic patients after a meal tolerance test, reaching a nadir of 69% of the basal level after the meal. Circulating plasma ghrelin showed a diurnal pattern with preprandial increases, postprandial decreases, and a maximum peak at 0200 h. This study demonstrates that nutritional state is a determinant of plasma ghrelin in humans. Ghrelin secretion is up-regulated under conditions of negative energy balance and down-regulated in the setting of positive energy balance. These findings suggest the involvement of ghrelin in the regulation of feeding behavior and energy homeostasis.
(Shiiya et al., 2002). An inverse pattern of ghrelin and insulin levels has been described during 24-h observation in normal subjects (Cummings et al., 2001). Insulin is a physiological and dynamic modulator of plasma ghrelin, and evidence that insulinaemia possibly mediates the effect of nutritional status on its concentration has been observed during hyperinsulinaemic-euglycemic clamp studies (Saad et al., 2002). A study that evaluated ghrelin concentrations in normal vs. type 1 diabetics revealed that insulin is required for prandial ghrelin suppression in humans (Murdolo et al., 2003). Recent literature suggests an inverse relationship between fasting ghrelin and insulin levels and insulin resistance indices (Purnell et al., 2003; McLaughlin et al., 2004; Schofl et al., 2002). The data in the pediatric literature on the influence of nutrient consumption and insulin resistance on plasma ghrelin is controversial. One study reported no suppression of ghrelin after feeding in children, suggesting a peculiar functional profile of the ghrelin system in childhood. In contrast, in obese Japanese children (Ikezaki et al., 2002), and in Pima Indian children (Bunt et al., 2003), ghrelin levels inversely correlated with fasting insulin and insulin resistance indexes. In a study to evaluate the role of ghrelin in childhood obesity, a state associated with hyperinsulinism and insulin resistance, Bacha and Arslanian noted significantly lower fasting ghrelin levels in overweight children compared to normal weight children and ghrelin suppression after OGTT was seen to be modulated by insulin sensitivity independent of adiposity (Bacha et al., 2005).

4.6 Ghrelin in Children and the Relation to Race

African-American (AA) children have lower absolute and percent suppression in ghrelin levels in response to feeding, compared with their American white (AW) peers (Bacha et al., 2006). Ghrelin suppression in AA children appears to be resistant to the effect of insulin in lowering ghrelin. The lower suppression of ghrelin in AA correlates with insulinaemia and insulin resistance. In addition, AA children have lower fasting and postprandial levels of peptide YY (PYY), but PYY does not correlate with insulin sensitivity. This alteration in PYY levels and meal-induced ghrelin suppression could be responsible for differences in hunger and/or satiety between AA and AW children and could be a potential mechanism of race-related differences in hunger/satiety predisposing to risk of obesity and increased risk of obesity in blacks (Bacha et al., 2006).

5 Obestatin

Obestatin, a recently identified 23-amino acid peptide hormone, has been reported to bind to and activate the orphan receptor, G protein-coupled receptor-39 (GPR39) (Zhang et al., 2005; McKee et al., 1998). Obestatin is generated from proteolytic cleavage of preproghrelin. It inhibits food intake and gastrointestinal motility but does not modify in vitro GH release from pituitary cells. Obestatin exhibits opposite effects of ghrelin on energy homeostasis and gastrointestinal function (Zhang et al., 2005). Therefore, it has been postulated to antagonize ghrelin’s actions on energy homeostasis and gastrointestinal function.

5.1 Circulating Obestatin Levels

Obestatin secretion is pulsatile and displays an ultradian rhythmicity, very similar to ghrelin and GH secretion (Zizzari et al., 2006). Obestatin is involved in the regulation of appetite and body weight in antagonistic fashion to ghrelin, both deriving from a common precursor peptide. Though obestatin and ghrelin are derived from the same gene, lack of strict correlation in their levels supports the notion that obestatin is a physiologically relevant peptide and not only a nonfunctional connective peptide. Such a
The hypothesis is further substantiated by the differential effect of fasting on ghrelin and obestatin levels, ghrelin being markedly increased and obestatin slightly decreased after 24 h of fasting. This strongly suggests that the secretion of the two peptides is regulated by the nutritional status in an opposite manner (Zizzari et al., 2006). Controversies still exist on the definite effects of obestatin on food intake/energy balance as well as on the measurements of the hormone levels in the human blood (Garg, 2007). Obese patients show decreased fasting plasma ghrelin levels (Guo et al., 2006; Tschop et al., 2001) that increased after weight loss following gastric banding (Haider et al., 2006). Therefore literature data show parallel changes in ghrelin and obestatin secretion in pathological conditions characterized by energy imbalance, suggesting that dysregulated metabolic states may potentially affect the preproghrelin gene expression and/or the splicing of its products and that the conclusive effect on food intake and energy homeostasis could depend upon the ratio between ghrelin and obestatin peptides (Monteleone et al., 2008). Mechanisms responsible for such an imbalance of ghrelin/obestatin ratio are not clear, because little is known about the posttranslational cleavage of the preproghrelin peptide (Monteleone et al., 2008). Very little is known about obestatin's physiological role in humans. In morbidly obese patients, a rise in fasting serum obestatin was reported (Haider et al., 2006) after invasive gastric banding surgery and subsequent weight loss. Plasma obestatin levels were found to be higher in children with the Prader-Willi syndrome than in matching controls (Butler et al., 2007), conflicting with another report that found similar fasting levels that did not change during an oral glucose tolerance test (Park et al., 2007). A study in obese and lean humans (60) showed a postprandial suppression of both plasma obestatin and ghrelin compared with the fasting state. After the ingestion of a meal, the combined increase in plasma glucose and insulin could account for the decrease in plasma ghrelin and obestatin levels. Insulin reduces plasma ghrelin in non-diabetic patients and, to a relatively lesser extent, also in insulin-resistant type 2 diabetic patients at very high supra physiological insulin concentrations (Anderwald et al., 2003). In contrast to the data on ghrelin, information concerning the action of insulin on plasma obestatin is still lacking in humans. Since salivary ghrelin and obestatin levels correlated with the blood levels, it was suggested that determination of salivary values could represent a non-invasive alternative to serum ones that can be useful in clinical practice (Ozbay et al., 2008).

5.2 Obestatin and Insulin Resistance

In a study in adult humans, decreasing concentrations of obestatin were associated with diabetes and impaired glucose regulation and the insulin sensitivity surrogate homeostasis model assessment (HOMA) of insulin resistance (Qi et al., 2007). In a different study, plasma obestatin is reduced by insulin in insulin-sensitive but not in insulin-resistant persons. No significant association was found when correlating HOMA with fasting obestatin concentrations (Park et al., 2007) in subjects with Prader-Willi Syndrome. Fasting plasma concentrations of obestatin, but not ghrelin, are reduced in insulin resistance and are directly associated with whole body insulin sensitivity in non diabetic humans. Furthermore, plasma obestatin is reduced by insulin in insulin-sensitive but not insulin-resistant persons (Anderwald-Stadler et al., 2007).

6 Conclusions

The prevalence of childhood obesity is increasing worldwide, along with diabetes and other obesity-associated morbidities. The hormones leptin, ghrelin and obestatin are known to affect the development
of obesity by influencing food intake, fat metabolism, and gastrointestinal function. Serum levels of one or more of these hormones have been found to correlate with obesity measures such as body mass index, amount of fat mass, and waist circumference, as well as with insulin concentration and insulin resistance. Congenital deficiencies of leptin and ghrelin demonstrate the profound effect these hormones have on food intake, fat metabolism, and growth. Thus, they appear to offer promise for the development of new strategies to treat obesity in both children and adults. Development of effective treatments will require more complete knowledge about the production, regulation, and functions of these hormones.

Conflict of Interest Statement

The author declares that the preparation of the book chapter was carried out in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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