Children’s Obesity is a Global Epidemic and Associated with an Increased Risk of Hypertension, Diabetes Mellitus, and Coronary Heart Disease, in Addition to Psychological Disorders. Interventions such as Bariatric Surgery Are Highly Invasive and Lifestyle Modifications Are Often Unsuccessful Because of Disturbed Perceptions of Satiety. New Signaling Peptides Discovered in Recent Years That Are Produced in Peripheral Tissues Such as the Gut, Adipose Tissue, and Pancreas Communicate with Brain Centers of Energy Homeostasis, Such as the Hypothalamus and Hindbrain. This Review Discusses the Major Known Gut- and Adipose Tissue-Derived Hormones Involved in the Regulation of Food Intake and Energy Homeostasis and Their Serum Levels in Childhood Obesity Before and After Weight Loss as Well as Their Relationship to Consequences of Obesity. Since Most of the Changes of Gastrointestinal Hormones and Adipokines Normalize in Weight Loss, Pharmacological Interventions Based on These Hormones Will Likely Not Solve the Obesity Epidemic in Childhood. However, a Better Understanding of the Pathways of Body Weight- and Food Intake-Regulating Gut- and Adipose Tissue-Derived Hormones Will Help to Find New Strategies to Treat Obesity and Its Consequences.


Research on Energy Homeostasis Regulation in Children Is Increasingly Important As Obesity Is the Most Important Risk Factor for the Development of the Metabolic Syndrome and Type 2 Diabetes Mellitus (T2DM) in Youth, and the Rise in Childhood Obesity and Childhood T2DM Are Nearly Statistically Parallel. In 2006, the Prevalence of Obesity in US Children Reached 17%, and If Current Trends Continue, Childhood Obesity May Reach 20% by 2010. Pediatric Endocrinology Is Experiencing a Wave of Newly Identified Signaling Peptides Illuminating the Gut-Brain Axis Regulating the Body’s Energy Balance, or More Thoroughly Described as the Gut-Central and Peripheral Nervous Systems–Accessory Organ (Eg, Pancreas, Liver) Axis. Gut Hormones (Enterokines) and Adipose Tissue-Derived Signaling Molecules (Adipokines) Interact with Brain Centers in Complex, Overlapping Mechanisms of Energy Intake and Storage. These Mechanisms Evolved During Long Periods of Hunger in the Evolution of Man to Protect the Species from Extinction. However, Today’s Modern Sedentary Lifestyle Has Turned This Evolutionary Advantage of Storing Energy as Fat into a High Risk of Cardiovascular Morbidity and Mortality. To Complicate Matters, Although Body Weight Is Precisely Regulated, Long-Term Nutrient Excess May Change Set Points of the Body Energy Balance Including the Gut-Brain and the Adipose Tissue–Brain Axes. In Cases of Obesity, This Appears to Make It Even More Difficult to Reduce Overweight, As Active Species-Protecting Defense Mechanisms Maintain an Elevated Level of Body Fat.

Understanding the Changes That Occur in the Particular Regulators of Homeostasis—Hormones and Peptides—Relative to the Timing and Method of Weight Reduction in Overweight Children Is Fundamental to Understanding Pediatric Obesity. We Examined These Homeostatic Regulators Before and After Weight Loss Due to Lifestyle Intervention.
after weight reduction in a 1-year lifestyle intervention “Obeldicks.” Briefly, this program is based on physical exercise (1 year), nutrition education and behavior therapy for children and parents separately (first 3 months), and individual psychological care of the child and his or her family (months 4–9). The exercise therapy consists of sports, instruction in physical exercise as part of everyday life, and reduction of the amount of time spent watching television. The nutritional course is based on the prevention concept of the “optimized mixed diet,” which is both fat and sugar reduced containing 30% energy intake fat, 15% energy intake proteins, and 55% energy intake carbohydrates including 5% energy intake sugar. This lifestyle intervention was effective to reduce overweight over a period of at least 3 years after intervention and improved cardiovascular risk factors such as dyslipidemia, impaired glucose tolerance, and hypertension. Furthermore, the intima-media thickness as a predictor of early cardiovascular changes was reduced in children who participated in this intervention. All these findings proved the clinical relevance of the achieved weight loss.

This article will discuss the major known gut- and adipose tissue–derived peptides involved in the regulation of food intake and energy homeostasis, including changes in some of these signaling molecules observed during weight gain and loss in obese children participating in lifestyle interventions, and describe clues that may be helpful in both short-term and long-term management and treatment of childhood obesity.

MODULATORS OF HUNGER AND SATIETY FROM THE PERIPHERY (GASTROINTESTINAL TRACT AND ADIPOSE TISSUE)

The discovery of the adipose tissue–derived hormone leptin in 1994 elucidated an important negative feedback mechanism of energy balance and how information about energy stores is conveyed to the central nervous system. This and other feedback mechanisms of energy metabolism have been intensively studied in rodent models. They demonstrate that peptides produced in the periphery, such as adipose tissue hormones (leptin, resistin, adiponectin, visfatin, retinol-binding protein 4) and appetite-restraining hormones from the gastrointestinal tract (peptide tyrosine-tyrosine [PYY], glucagon-like peptide 1 [GLP-1], oxyntomodulin, cholecystokinin) and pancreas (insulin, pancreatic polypeptide [PP], amylin), as well as the hunger-mediating hormone ghrelin, are important afferent signals that bind to receptors in the hypothalamus and hindbrain (Figure).

Gastrointestinal Peptides

Ghrelin is a peptide containing 28 amino acids and was identified in 1999 as a ligand for the secretion of growth hormone secretagogue receptor10 (Table). Ghrelin is produced principally by the stomach and, to a lesser extent, the duodenum25 and is the only known circulating orexinogen. Endogenous levels of ghrelin increase before meals and decrease after food intake, suggesting its role in both meal initiation and weight gain. It has been postulated that both the hyperphagia and potentially the growth hormone deficiency in Prader-Willi syndrome may be related to ghrelin dysregulation, as high circulating levels of ghrelin have been observed in this disorder. Less clear is why serum ghrelin levels are decreased in nonsyndromic simple obesity, which may be due to overfeeding and a consequence of metabolic changes associated with obesity, such as insulin resistance.

Important clues about why some children and not others are successful in maintaining long-term weight loss have been shown in recent studies. Specifically, increased ghrelin levels during weight reduction are considered to be a compensatory mechanism responsible for making weight reduction unsustainable. Krohn et al11 showed that the increase of ghrelin levels after weight loss in obese children is correlated with an increase in insulin sensitivity. In a Spanish study of obese children on a calorie-restricted diet, ghrelin levels increased significantly after 3 months of successful weight reduction. In the Obeldicks lifestyle intervention, we found no significant changes in ghrelin levels in the children who achieved substantial weight reduction. A slow reduction of weight that does not cause an immediate compensatory increase of ghrelin may help stabilize and maintain a lower body weight and prevent a fast regain of weight due to an increase of ghrelin. These are encouraging results because ghrelin is the only known circulating appetite stimulant.

Obestatin is a recently identified peptide derived from the same gene (preproghrelin) as ghrelin and has the opposite effect on weight status, inhibiting food intake and gastrointestinal motility. Obestatin is postulated to antagonize ghrelin’s actions on homeostasis and gastrointestinal function. Because obestatin and ghrelin are both derived from the same gene, one study hypothesized a possible cause of obesity to be an imbalance of circulating obestatin and ghrelin levels. Preprandial ghrelin to obestatin ratios were elevated in obese subjects compared with controls, suggesting that a higher ratio may be involved in the etiology and pathophysiology of obesity; however, results from other studies are not conclusive.

A short-term summer camp weight reduction study of 46 obese children demonstrated increased ghrelin and obestatin levels and ghrelin to obestatin ratios after weight reduction. In Obeldicks, obestatin levels increased significantly after weight reduction while ghrelin levels did not change significantly, a pattern that may be important to stabilize the lower body weight and prevent recurrence of weight gain.

Peptide YY is a 36–amino acid peptide originally isolated and characterized in 1989 (Table). There are 2 endogenous forms, PYY1-36 and PYY3-36, abundant in humans. Peptide YY is a gut-derived hormone released postprandially by the L cells of the lower intestine that inhibits gastric acid secretion and motility through neural pathways. Peptide YY belongs to the family of peptides that includes neuropeptide Y and PP, which mediate their effects via G protein–coupled neuropeptide Y2, Y4, Y5, and Y6 receptors and display different tissue distributions and functions. PYY1-36 binds to all known Y receptor subtypes, whereas PYY3-36 shows affinity for the Y1 and Y5 receptor subtypes and high affinity for the inhibitory Y2 receptor subtype. PYY3-36 binding to the Y2 receptor subtype inhibits the orexigenic neuropep-
tide Y in the hypothalamus, causing short-term inhibition of food intake, especially high-fat meals.8-54 Studies in rodents identified the hypothalamus, vagus, and brainstem regions as sites of action.55 Functional magnetic resonance imaging of normal-weight humans infused with PYY3-36 to circulating concentrations similar to those observed postprandially showed modulated neuronal activity within the hypothalamus, brainstem, and midbrain regions involved in food reward processing.56 This suggests that PYY3-36 affects feeding by action on homeostatic and hedonic brain circuits.57 Peptide YY may also affect energy expenditure.58 Among other studies confirming this effect,59 peripheral infusion of PYY3-36 in humans showed increased energy expenditure and fat oxidation rates.60

In obese children, levels of the anorexigenic hormone PYY are low. After efficient weight loss in Obeldicks, PYY levels significantly increased, reaching levels comparable with normal-weight individuals.54 Once effective weight loss has been achieved, the anorectic effect of PYY may help stabilize weight and thereby prevent later weight gain in patients whose PYY levels increased to normal levels.

Glucagon-like peptide 1 is a gut hormone synthesized from enteroendocrine L cells of the small and large intestine and secreted in 2 major molecular forms, GLP-13-36 amide and GLP-17-37, with equipotent biological activity (Table). Glucagon-like peptide 1 binds receptors in key appetite-related sites in the hypothalamus (eg, arcuate and dorsomedial nuclei) and the brainstem (specifically the nucleus of the solitary tract).15,61,62 It is the most potent insulin-stimulating hormone known to date, it suppresses glucagon secretion, and it inhibits gastric emptying and acid secretion. In obese children, an attenuated GLP-1 response may contribute to impaired insulin response, leading to T2DM.61-63 Glucagon-like peptide 1 may also reduce energy intake and enhance satiety, likely through the aforementioned delay of gastric emptying and specific GLP-1 receptors in the central nervous system. Its role in childhood obesity is poorly understood, with contradictory post–weight loss level changes reported in the literature.15-18,61-68

Obese children participating in Obeldicks showed significant decreases in GLP-1 levels. At baseline, GLP-1 lev-

Figure. Peripheral regulators and important brain areas of energy homeostasis. Long-term regulators are adipose tissue–derived food intake–inhibiting hormones leptin and adiponectin, whereas hormones produced in the gastrointestinal (GI) tract and pancreas are short-term food intake–inhibiting (peptide tyrosine-tyrosine [PYY], glucagon-like peptide 1 [GLP-1], oxyntomodulin [OXM], cholecystokinin [CCK], pancreatic polypeptide [PP], amylin) or stimulating (ghrelin) signals. Intact lines connect to the hypothalamus (pink); dashed lines, to the hindbrain (blue, solitary tract nucleus).
els did not differ significantly between obese and lean children. The glucose levels remained static and the decreases in GLP-1 levels were significantly correlated with decreases in insulin levels and insulin resistance index scores.16

Oxyntomodulin is a 37–amino acid peptide that, like GLP-1, is a product of the preproglucagon gene (Table). It is released into the circulation system postprandially and when administered either centrally or peripherally in rodent models or peripherally in humans reduces food intake.19 Oxyntomodulin is equally effective as GLP-1 at inhibiting food intake even though it is thought to do so through a different pathway.

Cholecystokinin was the first gut hormone implicated in the control of appetite by reducing food intake.21 Cholecystokinin is a meal termination signal released postprandially from the gastrointestinal tract (mostly upper small intestine), reducing both meal size and meal duration. After eating, cholecystokinin levels remain elevated up to 5 hours and stimulate gall bladder contraction, pancreatic enzyme release, and intestinal motility, which in turn affect gastric emptying. The alimentary cholecystokinin receptor, CCK_b, is present on the vagus nerve, enteric neurons, brainstem, and dorsomedial nucleus of the hypothalamus. Cholecystokinin likely mediates its effect on appetite regulation by crossing the blood-brain barrier where it acts on receptors in the dorsomedial nucleus of the hypothalamus to reduce levels of neuropeptide Y, a potent appetite-stimulating peptide. However, studies in children are missing so far.

Pancreatic Hormones and Peptides

Insulin plays an extremely important role in energy homeostasis (Table). Insulin receptors are expressed in different hypothalamic nuclei. After passing the blood-brain barrier, insulin exerts appetite-inhibiting effects. In rodents, it was proven that insulin administered intracerebroventricularly inhibits food intake by activation of the insulin receptor substrate–phosphatidylinositol 3-kinase (IRS-PI3K) pathway in ventromedial neurons of the hypothalamus.68,70 Numerous insulin knockout models show that decreased central insulin effect leads to the obese phenotype. Most recent research results show that central insulin resistance can be caused by hypothalamic inflammation due to nutrient excess,71 causing reduced IRS-PI3K signaling, which thereby contributes to increased appetite and the maintenance of elevated body weight.72 In childhood obesity, increased blood insulin levels indicate peripheral and central insulin resistance. Successful reduction of overweight leads to reduction of hyperinsulinemia and improved insulin sensitivity.22,23

Pancreatic polypeptide is a 36–amino acid peptide produced under vagal control by peripheral cells of the endocrine pancreatic islets, and to a lesser extent in the exocrine pancreas, colon, and rectum, in response to a meal and insulin-induced hypoglycemia (Table).47,73 Administration of pharmacological doses of PP in humans decreases food intake for 24 hours74 and inhibits the gastric emptying rate, exocrine pancreatic secretion, and gallbladder motility.73

Changes in PP levels and their relation to the anorexigenic hormones insulin and leptin were studied in Obeldicks.23 At baseline, obese subjects had lower PP concentrations compared with lean controls.25 Following lifestyle intervention, PP concentrations significantly increased and tended to normalize in the children who achieved substantial weight loss in comparison with children who did not lose weight.25 Yet, the changes in PP concentrations did not significantly correlate to changes of insulin and leptin concentrations.25

Amylin is a 37–amino acid polypeptide synthesized and released together with insulin by the pancreatic beta cells.
in response to nutritional input and contributes to glycemic and appetite control (Table). Amylin is a satiety peptide, causing a reduction of the meal size and inhibition of gastric emptying. In addition, amyloid depositions that have been detected in pancreatic islets of T2DM play a central role in the development of beta-cell failure in T2DM.

In obese children, amylin levels were significantly higher as compared with lean controls. Substantial weight loss in Obeldicks led to a significant decrease of amylin concentrations. Moreover, the increase of amylin levels in childhood was related to hypersecretion of insulin.

Hormones Secreted by Adipose Tissue and Cytokines

Adipose tissue is not only important in energy storage, but it is also very active in producing hormones and cytokines (adipokines), which play a role in the pathogenesis of obesity-associated illnesses. Proinflammatory adipokines produced in adipose tissue are leptin, resistin, plasminogen activator inhibitor-1, interleukin 6, and tumor necrosis factor α. Several studies demonstrated higher levels of inflammatory markers in obese children than in normal-weight children and some of these could be normalized by lifestyle intervention. Adipokines are a possible link between insulin resistance and adiposity. The production of interleukin 6 leads to the increase of C-reactive protein, which represents a cardiovascular risk factor.

Leptin is a 167-amino acid peptide formed in adipose tissue, forwarding information regarding energy supply and peripheral energy storage in adipose tissue to the brain, specifically the hypothalamus (Table). Leptin production is stimulated by insulin and glucocorticoids. The leptin receptor is a single-transmembrane domain receptor of the cytokine receptor family, which activates Janus kinase2 in the signal transduction pathway and like insulin, activates IRS-PI3K in neurons of the ventromedial hypothalamus, whereby it induces central appetite inhibition and stimulates energy expenditure by increasing the central sympathetic tone. A high density of leptin receptors was found in the hypothalamic arcuate nucleus and the ventromedial hypothalamus nucleus. Leptin has a soluble receptor that represents the main binding site for leptin in blood and may be a negative regulator of free leptin. Leptin's homeostatic effect is anorexigenic, invoking satiety and ceasing nutritional intake. Leptin levels circulating in the blood correlate with the amount of adiposal tissue mass. Although it would seem that increased levels of leptin in overweight individuals would lead to appetite suppression and lower food intake, this does not occur because increased fat mass also leads to leptin resistance and decreased leptin signaling in the brain. This resistance then may lead to ineffective appetite inhibition and changes the set point of energy homeostasis, resulting in a defense of a higher level of body fat. Leptin deficiency in obese individuals is very rare and is caused by a homozygous ob gene mutation. Only a few patients and families have been reported in the literature. In these individuals, leptin levels are low and leptin therapy has been proven to be a causal treatment of obesity. In most obese individuals, however, serum leptin levels are upregulated because of the increased fat mass and leptin resistance, and leptin levels fall after successful weight loss, while decreased serum soluble receptor concentrations in obese children increase after weight loss.

Adiponectin is synthesized and secreted exclusively by adipose tissue (Table). It exerts anti-inflammatory effects and appetite-restraining effects and counters insulin resistance, thereby offering protective mechanisms against the development of both T2DM and cardiovascular disease. Adiponectin also affects thermogenesis and adipoceptor receptors are expressed in various peripheral tissues, including muscle, liver, and hypothalamus. The central appetite-adjusting mechanisms of adiponectin are not yet fully understood. Interestingly, adiponectin levels are reduced in states of obesity and T2DM. Adiponectin has anti-inflammatory properties and negatively correlates with cytokine levels and insulin resistance. Low adiponectin levels might play a role in the development of the metabolic syndrome and cardiovascular disease.

In Obeldicks, adiponectin levels significantly increased and insulin resistance significantly improved in a parallel manner in the children who lost weight. In an even more recent study, Jeffery et al also studied this negative correlation of adiponectin levels in obese children and its role in mediating cardiovascular disease in children. They found clear links between adiponectin and features of the metabolic syndrome.

Resistin is another hormone secreted by adipose tissue and is involved in insulin sensitivity. It has been shown to modulate both glucose tolerance and lipid metabolism in vivo and in vitro. Although some data are contradictory, it seems that insulin might inhibit resistin secretion; however, recent animal models show that insulin is not the major regulator of resistin.

Two longitudinal adult analyses reported serum resistin changes to be positively correlated with changes in fat mass or weight loss yet other adult studies reported no correlations. Resistin serum levels were studied in obese children after 1 year of weight loss. Girls demonstrated higher resistin concentrations than boys, but there were no differences of resistin levels between lean and obese children, and there were no significant changes after weight loss. Retinol-binding protein 4 (RBP4) is a recently identified adipokine secreted primarily from adipose tissue with some secretion by the liver. It is a proposed link between obesity and insulin resistance. In normal mice, elevated RBP4 levels caused insulin resistance in muscle and increased hepatic gluconeogenesis, whereas RBP4 gene knockout mice had increased insulin sensitivity. In adults and children, RBP4 levels have been correlated with insulin resistance. Two recent studies showed that lifestyle intervention almost reversed elevated RBP4 levels in obese children. In our lifestyle intervention, children with substantial weight loss demonstrated a significant decrease of RBP4 levels in a parallel manner to blood pressure and triglycerides and insulin levels. These data suggest a link between RBP4, obesity, and markers of the metabolic syndrome. Visfatin/NAMPT is a recently identified adipocytokine from visceral fat that was found in higher concentrations in obese than in nonobese children. Visfatin, originally named pre-B cell colony-enhancing factor, is from the same gene that encodes nicotinamide 5-phosphoribosyl-1-pyrophosphate transferase (NAMPT), an en-
zyme important in mammalian nicotinamide adenine dinucleotide (NAD$^+$) biosynthesis. The relationship between visfatin/NAMPT and the parameters of glucose metabolism and insulin resistance is uncertain because of contradicting data potentially attributed to differences in immunoassay specificity. Recent evidence indicates haplo deficiency and chemical inhibition of NAMPT may cause defects in NAD$^+$ biosynthesis. Alterations in NAD levels could alter activities of important enzymes in metabolic pathways such as glycolysis or fatty acid oxidation in pancreatic beta cells.

**SOME EXAMPLES OF PHARMACOLOGICAL APPROACHES**

After the appetite-inhibiting effect of leptin had been discovered, it was hoped that administration of leptin might be a cure for obesity. The attempts were disappointing, mostly because simple obesity results in leptin resistance. Only in very rare patients with congenital leptin deficiency does leptin treatment lead to a strong long-term reduction of overweight. Some of the gut hormones, such as GLP-1 and CCK, have a very short half-life of a few minutes in the circulation because of rapid degradation, thus limiting their use as antiobesity drugs. However, exendin-4 is a long-acting GLP-1 receptor agonist that has recently been approved by the US Food and Drug Administration for the treatment of T2DM and has also been associated with weight loss. Preliminary data from rat models suggest that oxyntomodulin may be useful in treating obesity. One such rodent study suggested that oxyntomodulin exerts its anorectic effect through the GLP-1 receptor, as it was ineffective in GLP-1 receptor knockout mice. In a recent 4-day human study, oxyntomodulin not only promoted weight loss but increased energy expenditure by more than 25%.

GLP-1 and the amylin analogue pramlintide appear to decrease weight in patients with T2DM, which is an important secondary goal in treating these patients. Pharmaceutical studies have recently been performed to explore amylin’s therapeutic potential for treating both obesity and diabetes. Traditional pharmacotherapies to treat T2DM often exacerbate obesity, undermining any benefits of improved glycemic control as well as patients’ compliance with the treatment. The addition of leptin after amylin pretreatment elicited even greater weight loss compared with both monotherapy conditions, providing both nonclinical and clinical evidence that integrated neurohormonal approaches to obesity pharmacotherapy may facilitate more successful weight loss by emulating naturally occurring synergies. Administration of PYY in obese humans has been reported to reduce food intake in the short-term. Several gut hormone–based treatments for obesity are under investigation in phase 2 and 3 clinical trials, and many more are in the pipeline. These gut peptides need to be injected. Orally active inhibitors of the incretin-degrading enzyme dipeptidyl peptidase-IV offer an alternative.

**CONCLUSIONS**

Probably the most important conclusion to be made from the data presented herein is that the pathologies affect-
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