Obesity and Weight Regulation

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Childhood obesity is a global epidemic and rising trends in overweight and obesity are apparent in both developed and developing countries. Available estimates for the period between 1980 and 1990 show that the prevalence of overweight and obesity in children increased by a magnitude of two to five times in developed countries, and up to almost four times in developing countries. Therefore the current situation requires a population health approach. This has led to recommendations from experts that focus prevention initiatives on the goal of promoting healthy eating, active living and positive self-esteem rather than the achievement of ideal body weight [1].

Traditionally, public health strategies have focused on the individual, promoting healthy food choices and regular physical activity. However, the problem of rising obesity prevalence does not appear to be owing to a lack of interest by the individuals in the population. Recent reviews suggest that a paradigm shift, which considers the environment in which these individuals make choices on food consumption and engagement in physical activity, is necessary to understand and tackle the problem. In a supplement to *Obesity Reviews* a review of the literature on childhood obesity prevention was undertaken [1]. More than 13,000 reports which describe the programs to promote healthy weights in children have been reviewed. The goal of this synthesis was to develop best practice recommendations based on a systematic approach to finding, selecting and critically appraising programs addressing prevention and treatment of childhood obesity and related risk of chronic disease. A special focus was made on the issue for immigrant and minority populations [1]. In addition, a group of 65 physicians and other health professionals developed a consensus statement and recommendations for the problem of childhood obesity which has been published in *The Journal of Clinical Endocrinology and Metabolism* [2]. For the yearbook selection this year, only articles published in journals with an impact factor of more than 2 were considered, assuming that relevant findings were published in these journals [3]. The top findings of the last year again reflect the high quality of research in this field.

Food for thought

Prevalence of overweight in children with developmental disorders in the continuous National Health and Nutrition Examination Survey (NHANES) 1999–2002

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Background: Clinical observations lead to the hypothesis that children with developmental disorders would be at greater risk for overweight than their typically developing peers.

Methods: Within the continuous NHANES 1999–2002, the prevalence of overweight in children with developmental disorders was estimated. Four questions were used to identify children with these disorders. The 85th percentile for BMI was used to define at-risk-for-overweight and the 95th percentile for BMI was used as the definition for overweight.

Results: Children with limitations in physical activity were found to have a higher prevalence of at-risk-for-overweight and overweight. Girls with learning disabilities had a higher prevalence of overweight. These results were found significant after adjustment for age and race-ethnicity.

Conclusion: Considering several important limitations of the analysis, these findings may support the hypothesis that children with developmental disorders resulting in reduced physical activity might be at greater risk for overweight than healthy children.

There is only limited available literature on the prevalence of overweight in children with developmental disorders. By contrast, the high prevalence of overweight among children with genetically-related disabilities such as Prader-Willi syndrome, Down syndrome, congenital disabilities such as spina bifida, and some types of cerebral palsy is well documented. Children with developmental disorders or at least specific subgroups of these children might be at higher risk for overweight than their typically developing peers. The complex medical, physical and psychosocial difficulties that these children encounter may put them at higher risk for obesity. For example, dietary factors such as the use of food as a behavioral re-enforcer or mealtime behaviors that influence food choices may lead to an energy imbalance. In addition, the lack of physical activity opportunities might also increase weight gain. The report shows that children with physical activity limitations were significantly more likely to be at risk for overweight than those without physical activity limitations (50.9 vs. 30.6%, $p < 0.001$). These children were also more likely to be overweight. Interestingly, the prevalence of overweight was lower in boys with attention deficit disorders as compared to those without (12.7 vs. 18.2%, $p = 0.03$).

The issue studied in this investigation is important. Further research in this area is warranted for several reasons: first to better establish the prevalence of overweight in this population, second to elucidate the specific challenges that children with various developmental disorders face in the health promotion arena, and third to devise appropriate intervention strategies that take their particular needs into account. In addition, the more detailed investigation of specific subgroups of children with developmental disorders may also help to increase our understanding of mechanisms regulating hunger and satiety, physical activity and body weight.

Review

Being big or growing fast: systematic review of size and growth in infancy and later obesity

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Background: Obese children and adolescents are normally not born obese. However, recent studies show that the relationship between body weight at birth and postnatal weight gain might be more important for the risk of obesity later in life than originally suggested.

Methods: A systematic literature review in order to assess the association between infant growth and subsequent obesity was carried out. It was further investigated whether groups of infants with particular patterns of growth are at greater risk.

Results: 24 studies were found which met the inclusion criteria. Most of them assessed the relation between infant size and subsequent obesity showing that infants with higher body weights or with obesity were at increased risk of obesity during the following years compared with non-obese infants. Odds ratios or relative risks for subsequent obesity range from 1.35 to 9.38. A few studies assessed the relation of infant growth with subsequent obesity. Most studies showed that infants who grew more rapidly were at increased risk for obesity. Relative risks of later obesity range from 1.17 to 5.70.

Conclusions: Infants in the highest end of the distribution for weight and those who grow rapidly are at increased risk of obesity in childhood and adulthood.

This systematic literature review supports the hypothesis that increased body weight and faster growth during infancy and childhood are associated with an increase of obesity in later life. This overweight group comprises a third category beyond the two other previously recognized groups: the first includes infants with a low birth weight followed by rapid catch-up growth during early infancy which seems to be a risk factor for obesity and for the development of metabolic disturbances (insulin resistance, metabolic syndrome). The second group includes those with a normal birth

weight who show an early adiposity rebound which results in a greater risk for subsequent obesity. Observational reports suggest that the new and third group have fewer metabolic complications. The association of birth weight and childhood growth with later obesity have not yet been systematically assessed considering the whole weight and growth velocity distributions. Therefore, this study adds to the current knowledge that infants who are at the highest end of the distribution for weight or body mass index, or who grow rapidly during infancy, are at increased risk of subsequent obesity. There was no evidence to suggest that exposure at a particular time during infancy was critical. The associations found in the present analysis were consistent across a range of settings in developed countries, for obesity measured in childhood, adolescents, and early adulthood, and over time for people born from 1927 to 1994.

On the basis of the present results it would be important to assess whether factors influencing infant growth are amenable to change, to establish which strategies might alter infant growth, and to find out whether these are acceptable to parents. Scientific knowledge about effective obesity prevention measures to be taken with young children is still insufficient [4]. There is an urgent need to learn more about effective prevention in early childhood. These measures should aim to influence the eating and physical activity behaviors of young children and their families.

It has been known for some time that hormones extensively affect brain development. There might be critical periods in brain development early in life that may profoundly affect food intake and body weight. The recent finding that leptin can modulate both synapse numbers and synaptic activity in the NPY and POMC neurons in the hypothalamic arcuate nucleus [5] are consistent with the concept that under- and overnutrition during critical periods of high hypothalamic development may induce long-lasting and potentially irreversible effects into adulthood. Therefore, the development of taste and hunger, satiety perception and eating behavior during early life might be critical for later weight status.

The practical implications of these findings change a paradigm. In former times, pediatricians have had to focus on infant and childhood nutrition in order to increase weight gain and growth which for many years have been critical for health and survival in early years. Today, there might be a contrasting task for pediatricians on the other side of weight distribution and growth velocity of infants: the prevention of fast growth and increased body weights should be achieved by controlling energy intake and the quality of nutrients which might influence the development of taste and hunger, satiety perception and eating behavior [4].

Important for clinical practice: apple or pear?

Mesenteric fat thickness is an independent determinant of metabolic syndrome and identifies subjects with increased carotid intima-media thickness

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Background: Body fat distribution is critical for the obesity-related health risk. Increased visceral fat depots are associated with the metabolic syndrome, an increased risk for cardiovascular disease and type 2 diabetes. In this study the hypothesis whether mesenteric fat thickness was an independent determinant of metabolic syndrome was tested.

Methods: In 290 Chinese subjects an ultrasound examination for measurement of the thickness of mesenteric, preperitoneal, and subcutaneous fat as well as carotid intima-media thickness was performed.

Results: Mesenteric fat thickness had significant correlations with various metabolic variables. In a multivariate regression analysis, mesenteric fat thickness was an independent determinant of all components of the metabolic syndrome. For every 1-mm increase in mesenteric fat thickness the odds ratio of metabolic syndrome was increased by 1.35. A mesenteric fat thickness of ≥ 10 mm was the optimal cut-off value to identify metabolic syndrome with a sensitivity of 70% and a specificity of 75%.

Conclusion: The thickness of the mesenteric fat depot is an independent determinant of the metabolic syndrome. The measurement of mesenteric fat thickness by ultrasound examination helps to identify subjects with the metabolic syndrome and an increased carotid intima-media thickness.

Combined influence of body mass index and waist circumference on coronary artery disease risk factors among children and adolescents

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Background: The Bogalusa Heart Study and other surveys have shown that coronary artery disease (CAD) already starts early in childhood. Children with hypertension, insulin resistance, dyslipidemia and increased body weights have a higher risk for the development of CAD. Further studies in adults and children have revealed that increased visceral fat depots are the main risk factor for the development of the metabolic syndrome and CAD. The objectives of this investigation were to determine whether BMI and waist circumference have independent effects on CAD risk factors among children and adolescents. Furthermore, it should be assessed if the incorporation of waist circumference into the clinical practice may be of use to identify children and adolescents elevated CAD risk factors.

Methods: A cross-sectional sample of 2,597 individuals (5–18 years of age) out of the Bogalusa Heart Study was investigated. Outcome measures included seven CAD risk factors.

Results: BMI and waist circumference did not have independent effects on the risk factors. However, when BMI and waist circumference values were categorized with a threshold approach, waist circumference provided information on CAD risk beyond that provided by BMI alone. For example: in the overweight BMI category, the high-waist-circumference group had a two times higher risk for elevated triglyceride levels, high insulin levels, and the metabolic syndrome, compared with the low-waist-circumference group.

Conclusion: The results of these studies support the idea that a combination of BMI and waist circumference should be used in clinical settings to evaluate the presence of elevated health risk among children and adolescents.

Many studies mainly in adults have reported that visceral obesity or an abdominal or a central type of body fat distribution is associated with lipid disorders, increased serum insulin, increased uric acid concentrations, and elevated blood pressure. These findings have led to the assumption that visceral fat depots are an important link between obesity on the one side and the metabolic syndrome on the other. Measurement of waist circumference or waist-to-hip ratio in adults was already established 20 years ago for the estimation of the obesity-associated risk. Several studies in children and adolescents have shown that an abdominal or a central body fat distribution also reflects a risk factor already in this age period [6]. The present study by Janssen et al. goes one step further by providing evidence that also for clinical practice the measurement of waist circumference in addition to BMI significantly increases the information about the obesity-related health risk in children and adolescents. The study of Liu et al. shows that the thickness of the visceral fat depots measured by use of a new generation of ultrasound techniques provides important information about metabolic disturbances and interestingly also about the carotid intima-media thickness. Taken together, both studies suggest that the measurement of waist circumference in the clinical practice for evaluation of obesity-related health risk in children and adolescents is of value. Furthermore, as shown by Liu et al., ultrasound examination of the thickness of visceral fat may at least help to discriminate cut-off points for the presence of the metabolic syndrome in adults.

Long-term prospective and controlled studies demonstrate adipose tissue hypercellularity and relative leptin deficiency in the post-obese state

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Background: Obesity is characterized by an increase of adipose tissue mass. This increase results mostly from an increase in fat cell volume. Recent data however showed that in adults as in children the growth of adipose tissue when becoming obese is also achieved by the differentiation of new fat cells from precursor cells. In this respect it is interesting to investigate adipose tissue cellularity (the number of fat cells and fat cell volume) after significant weight loss in obese subjects.

Methods: 25 obese subjects and 25 control subjects were studied in this prospective case-control study lasting 3 years.

Results: After weight loss, marked decreases in fat cell volume, leptin secretion and serum leptin concentrations were found. The post-obese subjects had a 43% smaller fat cell volume, a 68% lower adipocyte leptin production and 54% lower serum leptin levels than control subjects, despite an almost identical percentage body fat in the two groups. Fat cell volume was directly proportional to leptin secretion and serum leptin concentrations.

Conclusion: The post-obese state is characterized by adipose tissue hyperplasia (a higher number of fat cells as compared to control subjects) and lower leptin production or a relative hypoleptinemia.

In the 1970s it was suggested that fat cell number is determined within sensitive periods of adipogenesis during childhood and adolescence, and cannot be changed during adulthood. Recent studies however have clearly shown that the number of adipocytes is able to increase in adults when they gain large amounts of weight due to adipose tissue enlargement. Adipose tissue of extremely obese subjects is characterized by an increased number of adipocytes and by an enlarged volume of these cells [7]. In the present study, adipose tissue cellularity after significant weight losses achieved either by lifestyle modification or bariatric surgery was investigated and was compared to control subjects matched with the study subjects according to their BMI and body fat percentage after weight loss. The obese subjects lost significant amounts of weight resulting in a reduction of mean BMI from 42.8 to 32.2 kg/m². The finding of hypoleptinemia in the post-obese state might be secondary to decreased leptin production. The decreased leptin production might be secondary to the relatively smaller fat cells among the post-obese subjects. Leptin production from adipocytes depends on their volume and on regulating hormones such as insulin [8]. The hypoleptinemia in the post-obese state might lead to a decreased satiety signal and a decreased energy expenditure resulting in a higher risk for regaining weight. Furthermore, it is possible that the small fat cells of weight-reduced subjects have a more pronounced ability to accumulate lipids than the larger cells of control subjects. Therefore, both findings together might represent a yet unsolved problem for the prevention of weight gain after weight loss in obese subjects. Additional treatment approaches such as application of leptin in the post-obese state and new drugs which might help to decrease adipocyte number after weight loss should be evaluated to solve this problem.

Adipocyte-specific overexpression of FOXC2 prevents diet-induced increases in intramuscular fatty acyl CoA and insulin resistance

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Background: Insulin resistance is associated with defects in insulin signaling and significant increases in intramuscular fatty acyl CoA levels. Insulin resistance plays a major role in the development of type 2 diabetes and may be causally associated with increased intracellular fat content. The aim of the present study was to investigate the role of FOXC2 (forkhead transcription factor) in diet-induced insulin resistance and intracellular fat accumulation.

Methods: Transgenic mice with adipocyte-specific overexpression of FOXC2 have been generated and have been characterized by using the hyperinsulinemic-euglycemic clamps. Furthermore, insulin signaling analysis has been performed in skeletal muscle samples.

Results: FOXC2 transgenic mice were protected against diet-induced obesity and glucose intolerance. Whole-body fat mass was significantly reduced in these animals under normal or high-fat diet compared with wild-type mice. FOXC2 transgenic mice were also completely protected from diet-induced insulin resistance and intramuscular accumulation of fatty acyl CoA. FOXC2 transgenic mice were protected from diet-induced hepatic insulin resistance.

Conclusion: These findings demonstrate that FOXC2 transgenic mice are protected from diet-induced insulin resistance in skeletal muscle and liver.

Human winged helix/forkhead transcription factor gene (FOXC2) has been shown to be expressed in adipocytes and plays a key regulatory role in adipocyte metabolism [9]. Adipocyte-specific overexpression of FOXC2 has been shown to protect against diet-induced obesity and glucose intolerance. These effects were associated with increased expression of genes associated with adipocyte metabolism (e.g., uncoupling protein-1) and enhanced sensitivity of the β -adrenergic/cAMP/protein kinase A pathway. In addition, increased number and size of adipocyte mitochondria are also found in FOXC2 transgenic mice. These findings indicate an enhanced adipocyte metabolism in the transgenic mice. The changes in adipocyte metabolism result in less adiposity and normal glucose tolerance even following high-fat diet compared to the wild-type mice. Therefore, FOXC2 seems to be a novel therapeutic target for the treatment of insulin resistance and type 2 diabetes.

Increased intracellular fat disposition in muscle is a feature of insulin resistance. The findings of the current study support the notion that intramuscular accumulation of fatty acid metabolites (i.e., fatty acyl CoA) is the causative factor in the development of fat-induced insulin resistance. The mechanisms by which increased levels of fatty acid-derived metabolites cause insulin resistance involves activation of the serine kinase cascade, of which PKC- θ and/or inhibitor of κ B kinase- β (IKK- β) may play a role, leading to the serine phosphorylation of IRS-1 [10, 11].

Inhibition of p38MAPK increases adipogenesis from embryonic to adult stages

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Background: Mitogen-activated protein kinases (MAPK) are efficiently involved in cellular differentiation. The present study was carried out to clarify the role of p38MAPK in normal and pathological adipogenesis.

Methods: Adipose tissue samples from both dietary and genetically (ob/ob) obese mice were studied. In addition, various cell models were used to study adipocyte differentiation.

Results: Compared to adipose tissue samples from lean mice, p38MAPK activity was markedly decreased in the obese mice. Furthermore, p38MAPK activity was significantly higher in preadipocytes than in adipocytes. Inhibition of p38MAPK in vitro led to the following results: increased expression of adipocyte markers, increased phosphorylation of C/EBP- β and increased expression and transactivation of peroxisome proliferator-activated receptor (PPAR- γ).

Conclusion: By using these multiple approaches the data show that p38MAPK plays a negative role in adipogenesis via inhibition of C/EBP- β and PPAR- γ transcriptional activities.

Intracellular mitogen-activated protein kinase (MAPK) signaling pathways play a pivotal role in many essential cellular processes, such as proliferation, inflammation, and differentiation. The MAPK family comprises three groups: extracellular signal-regulated kinases (ERKs), c-Jun amino-terminal kinases (JNKs), and p38MAPK. In contrast to the results presented here, other studies using preadipocyte cell lines showed positive roles for p38MAPK in adipogenesis. These opposite effects in different cellular models demonstrate that the role of p38MAPK depends on the cellular models studied. Therefore, more physiological experimental models should be used in order to be sure about the physiological role of p38MAPK [7]. In addition, these observations presented here strongly suggest that the regulation of PPAR- γ by the p38MAPK pathway involves molecular patterns that are different in various cellular models. The demonstration that inhibition of p38MAPK results in the enhancement of both the expression and the activity of PPAR- γ could represent an interesting approach in the treatment of type 2 diabetes. Analysis of the in vivo effects of p38MAPK inhibitors regarding insulin resistance parameters and obesity should be of great interest. Keep in mind the close relationship between the adipose tissue, bone and cartilage, all developing from the same stem cell. A p38MAPK inhibitor was found to also reverse cartilage and bone destruction [12].

New treatment options

Randomized trial of lifestyle modification and pharmacotherapy for obesity

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Background: Comprehensive programs of diet, exercise, and behavior therapy are commonly applied for the treatment of obesity in children. By contrast, in adults weight loss medications are typically prescribed with minimal or no lifestyle modification. Both treatment approaches have limited therapeutic benefits. In both children and adults it is interesting to investigate a combined trial of lifestyle modification and pharmacotherapy for obesity. The aim of the present study was to investigate the combination of medication and group lifestyle modification in obese adults.

Methods: 224 obese subjects were involved in this 1-year trial. Subjects were randomly assigned to receive one of four different treatments: sibutramine alone (15 mg/day), lifestyle modification alone (high frequency of group meetings lasting 90 min following an established intensive program for weight control), combined therapy (sibutramine + lifestyle modification), and sibutramine + brief therapy (including homework assignments with daily food intake and activity records).

Results: Subjects who received combined therapy lost 12.1 ± 9.8 kg whereas those receiving sibutramine alone lost 5.0 ± 7.4 kg. Subjects treated by lifestyle modification alone lost 6.7 ± 7.9 kg and those receiving sibutramine + brief therapy lost 7.5 ± 8.0 kg.

Conclusion: The best weight loss results were obtained when pharmacotherapy was used in addition to a comprehensive program of diet, exercise, and behavior therapy.

The current practice of prescribing medications with minimal or no lifestyle modification limits the therapeutic benefits in adults. In obese children, a combination of lifestyle intervention and pharmacotherapy might be also more effective than lifestyle modification alone what safety data are accumulated and the drugs are approved. Current practice reveals an interesting contrast between treatment of obesity in children and adults. Whereas established programs for lifestyle intervention have been shown to be effective in subgroups of obese children [13] and pharmacotherapy is rarely used at this age group, medications are typically prescribed to adults with minimal or no lifestyle modification. These contrasting practices are incomprehensible since adults should be examples for the children with respect to healthy lifestyle.

Here, the combination of lifestyle modification, counseling and pharmacotherapy resulted in a significant loss of body weight. Nearly twice as many subjects in the combined therapy group as compared to the monotherapy groups lost 10% or more of their initial weight. Therefore, it is strongly recommended that weight loss medications, when approved, should only be used as an adjunct to a comprehensive program of diet, exercise, and behavior therapy. Further research is needed to identify effective methods of providing lifestyle counseling in primary care and community settings. The additive effect of pharmacotherapy and lifestyle modification should be evaluated in obese children and adolescents. Recent short-term studies report on a favorable safety profile of sibutramine and orlistat in children and adolescents [14, 15].

Peptide YY3-36 and glucagon-like peptide-17-36 inhibit food intake additively

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Background: Much work has been recently performed investigating the effect of exogenous administration of individual gut hormones on appetite to determine their potential physiological role in the control of food intake. The aim of the present study was to investigate the combined effects on appetite of peptide YY3-36 (PYY3-36) and glucagon-like peptide-17-36 (GLP-17-36). These hormones are secreted from intestinal L cells and plasma levels of both hormones rise physiologically after a meal.

Methods: Studies of co-administration of both peptides were performed in lean mice, genetically obese mice, in rats, and in human volunteers.

Results: The combination of both peptides led to a significantly greater feeding inhibition as compared to the effect of each peptide alone. These results were obtained in lean animals as well as in obese models. In addition, low doses of PYY3-36 and GLP-17-36 which alone had no effect on food intake led to a significant reduction in food intake when used in combination. Human volunteers receiving an infusion of both peptides on 4 separate days showed that energy intake from a buffet meal was reduced by 27% after combined PYY3-36 and GLP-17-36 treatment, being significantly lower than after either treatment alone.

Conclusion: PYY3-36 and GLP-17-36, which are physiologically co-secreted after a meal, may inhibit food intake additively. Since GLP-17-36 also stimulates insulin release and inhibits circulating glucagon, a combination of both peptides would be attractive for the treatment of patients with type 2 diabetes.

Glucagon-like peptide-1 (GLP1) is a hormone derived from the proglucagon molecule, and is secreted by intestinal L cells. It is the most potent stimulator of glucose-induced insulin secretion. A recent meta-analysis reported that infusion of GLP-17-36 was associated with a small dose-dependant reduction in energy intake in both lean and obese subjects [16]. Peripheral administration of GLP-17-36 inhibits food intake in man. Furthermore, GLP-17-36 and the GLP-17-36 receptor agonist exendin-4 also stimulate insulin release and inhibit circulating glucagon. The present results show that co-administration of PYY3-36 with GLP-17-36 significantly increases the reduction in energy intake from the buffet meal by 27%. Cumulative energy intake over 24h, including during a buffet meal, was reduced by 13%. Reduction in energy intake and increase in insulin secretion would make this combination a particularly attractive therapy for obese patients with type 2 diabetes.

Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects

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Background: Oxyntomodulin is released from the small intestine in response to food ingestion. The aim of the present study was to investigate whether self-administered subcutaneous oxyntomodulin would induce weight loss, and reduce appetite.

Methods: The injections were self-administered for 4 weeks, three times daily, 30 min before each meal.

Results: Body weight was reduced by 2.3 ± 0.4 kg in the treatment group compared with 0.5 ± 0.5 kg in the control group ($p = 0.0106$). This was achieved by a reduction in energy intake.

Conclusion: Subcutaneous self-administration of oxyntomodulin three times daily is able to reduce body weight and decrease food intake over a 4-week study period.

Several gut hormones have been found to modulate appetite [17]. Like the previously mentioned GLP-1, oxyntomodulin is a peptide product of the proglucagon gene released from the L cells of the small intestine in response to food ingestion. It also counts among the anorexigenic peptides along with cholecystokinin, polypeptide YY, GLP-1 and leptin. The preliminary data presented here suggest that the administration of oxyntomodulin could be an effective treatment for obesity. Currently available pharmacological agents for weight reduction affect widely distributed central neurotransmitter systems and may therefore have a broad spectrum of side effects. Mimicking postprandial satiety by administering a natural postprandial hormone such as oxyntomodulin may provide a more specific treatment for obesity.

Ghrelin: new exciting findings – new hope

Absence of ghrelin protects against early-onset obesity

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Background: Recent genetic studies have failed to show any significant defects or physiological alterations in adult ghrelin-deficient mice. The aim of the present study was to investigate very young ghrelin-deficient mice ($Ghrl^{-/-}$). They were exposed to a high-fat diet 3 weeks after weaning in an attempt to accentuate the phenotype of these mice.

Results: The results of the presented study show that male ghrelin-deficient mice exposed to a high-fat diet in early age maintain a lean phenotype in association with increased energy expenditure and locomotor activity. Despite the absence of ghrelin, these mice showed a paradoxical preservation of the GH/IGF-1 axis, similar to that reported in lean compared with obese humans.

Conclusion: These new data suggest that ghrelin plays an important role in regulating energy balance in young mice and an important role in the metabolic adaptation to nutrient availability.

Mice lacking ghrelin receptors resist the development of diet-induced obesity

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Background: Recent studies have reported an insignificant difference between ghrelin-knockout animals and wild-type controls in body weight. They also found no differences in cumulative food intake.

Methods: The aim of the present study was to characterize a novel ghrelin-receptor-null mouse model, in which ghrelin administration fails to acutely stimulate food intake or to activate arcuate nucleus neurons.

Results: Both female and male ghrelin-receptor-null mice eat less food, store less of their consumed calories, preferentially utilize fat as an energy substrate, and accumulate less body weight and fat mass than control mice. Ghrelin-receptor deletion also affected locomotor activity and levels of glycemia.

Conclusion: The data presented in this novel model of ghrelin-receptor-null mice supports the hypothesis that ghrelin-responsive pathways are important components of coordinated body weight control.

Ghrelin treatment reverses the reduction in weight gain and body fat in gastrectomized mice

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Background: In rats and humans more than 80% of the circulating ghrelin is lost following surgical removal of the stomach or the acid-producing part of the stomach. The aim of the present study was to investigate whether the effects of gastrectomy in mice can be reversed by long-term ghrelin treatment in these animals.

Methods: Ghrelin was given by subcutaneous injections for 8 weeks to young female mice subjected to gastrectomy 1 week previously. Control animals were subjected to sham operation.

Results: Injection of ghrelin after operation did not affect food intake as it was not affected by gastrectomy. Mean body weight was 15% lower in gastrectomized mice as compared to sham operated mice after 8 weeks. Daily injections of ghrelin during this time partially prevented this weight loss. Interestingly, the weight of fat was reduced in gastrectomized mice by 30%. This effect was reversed by ghrelin treatment. Ghrelin replacement also prevented the gastrectomy-induced decrease in lean body mass.

Conclusion: These findings suggest that ghrelin treatment can reverse the reduction in body fat and body weight observed in gastrectomized mice. These results are in line with the physiological role of ghrelin in the regulation of body composition.

Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake

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Background: Ghrelin is derived from a prohormone by posttranslational processing. Bioinformatic searches of putative hormones derived from a prepropeptide of known peptide hormones are an established method for identifying other hormones derived by posttranslational cleavage.

Results: On the basis of the bioinformatic prediction that another peptide deriving from proghrelin exists, a hormone from rat stomach was isolated and named obestatin. Treatment of rats with obestatin

led to suppression of food intake and gastrointestinal functions. In addition, obestatin treatment decreased body weight gain. Obestatin bound to the orphan G-protein-coupled receptor GPR39.

Conclusion: Two peptide hormones are derived from the same ghrelin gene. These hormones activate distinct receptors and have an opposing action in weight regulation.

Recent models with loss-of-function of ghrelin have raised doubts regarding the physiological significance of ghrelin in regulating food intake and energy expenditure [18–20]. Ghrelin-knockout mice have an insignificant difference in body weight and in cumulative food intake as compared to wild-type animals. The articles of Wortley et al. and Zigman et al. now offer a contrasting view to these negative results. It seems that ghrelin plays an important role in regulating energy balance in mice at very young ages and that ghrelin signaling is required for the development of the full phenotype of diet-induced obesity. Furthermore, the study by Dornonville de la Cours et al. supports a physiological role of ghrelin by showing that ghrelin replacement partially reverses the gastrectomy-induced reduction in body weight, lean body mass, and body fat. These results suggest that ghrelin is mainly involved in the control of fat metabolism.

The metabolic mechanism explaining this finding has to be investigated. Ghrelin stimulates the release of GH. However, in ghrelin-deficient mice on a high-fat diet, GH and GHR were not decreased to the same extent than in control animals on a high-fat diet. Therefore, the importance of endogenous ghrelin in regulating GH in vivo remains unclear. Otherwise ghrelin could potentially control fat metabolism via the metabolic actions of GH.

Some weeks ago, Pantel et al. report the identification of a GHSR missense mutation that segregates with short stature within 2 unrelated families [21]. This mutation, which results in decreased cell-surface expression of the receptor, selectively impairs the constitutive activity of the GHSR, while preserving its ability to respond to ghrelin. This first description, of a functionally significant GHSR mutation, which unveils the critical importance of the GHSR-associated constitutive activity, discloses an unusual pathogenic mechanism of growth failure in humans.

Finally, the discovery of obestatin and its receptor as a second hormone derived from the ghrelin gene makes the whole picture more complex. Ghrelin and obestatin activate distinct receptors and have an opposing action in weight regulation. Obestatin leads to a suppression of food intake and gastrointestinal functions as well as to a decrease in body weight gain in rats. At this time it can just be ascertained that this finding highlights the importance of posttranslational regulatory mechanisms.

Leptin: new developments

Long-term efficacy of leptin replacement in patients with generalized lipodystrophy

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Background: The lipodystrophies represent a group of clinical syndromes characterized by various degrees of adipocyte loss. Due to the loss of adipocytes, reduced adipokines including leptin are found. The aim of the present study was to investigate whether recombinant human leptin was able to reverse the severe metabolic features of generalized lipodystrophy as there are insulin resistance, dyslipidemia, and hepatic steatosis.

Methods: 15 patients with generalized lipodystrophy were treated with twice-daily recombinant methionyl human leptin (r-metHuLeptin) for 12 months.

Results: Reductions were seen in serum fasting glucose (from 205 ± 19 to 126 ± 11 mg/dl; $p < 0.001$), HbA1c (from 9 ± 0.4 to $7.1 \pm 0.5\%$; $p < 0.001$), triglycerides (from $1,380 \pm 500$ to 516 ± 236 mg/dl, $p < 0.001$), LDL (from 139 ± 16 to 85 ± 7 mg/dl; $p < 0.01$), and total cholesterol (from 284 ± 40 to

167 ± 21 mg/dl; $p < 0.01$). In addition, liver volumes were significantly reduced, representing loss of steatosis.

Conclusion: r-metHuLeptin led to significant and sustained improvements in glycemia, dyslipidemia, and hepatic steatosis.

This study introduces leptin as a first novel and effective long-term-treatment for severe forms of lipodystrophy. Leptin deficiency in lipodystrophy is a main factor responsible for the severe insulin resistance and other metabolic disturbances (e.g., dyslipidemia and liver steatosis) seen in affected patients. Recombinant leptin had a potent and sustained effect to reverse the severe metabolic features of generalized lipodystrophy. A natural question is whether leptin's ability to decrease food intake adequately explains the metabolic improvements seen. Several earlier reports suggest that the action of leptin is not mediated solely by reducing food intake. Leptin is believed to be crucial in mitochondrial function which likely accelerates the removal of ectopic fat in the liver and other organs. Further studies are needed to investigate the metabolic effect of leptin in different cell and organ systems.

Neonatal leptin treatment reverses developmental programming

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Background: An adverse intrauterine environment is associated with long-term metabolic consequences, in particular obesity, insulin resistance, and type 2 diabetes. The aim of the present study was to investigate the early leptin treatment in offsprings of rats subjected to undernutrition during pregnancy.

Methods: A previously developed maternal undernutrition model of fetal programming was used in this study. The effects of neonatal leptin treatment on the metabolic phenotype of adult female offspring were investigated.

Results: Leptin treatment from postnatal day 3 to 13 resulted in a transient slowing of neonatal weight gain, and normalized caloric intake, locomotor activity, body weight, fat mass, and fasting plasma glucose, insulin, and leptin concentrations. This was not seen in saline-treated offspring of undernourished mothers who developed obesity, hyperinsulinemia, and hyperleptinemia.

Conclusion: The present study demonstrates that all the measured metabolic consequences of maternal undernutrition were reversed by a period of neonatal leptin treatment in female rats.

The current findings indicate that at least in the rat, there is an early postnatal window during which the process of developmental programming can be reversed. SGA (small for gestational age) children have been shown to have low cord blood and plasma leptin levels and a predisposition to develop the metabolic syndrome in adult life. The mechanisms underlying the developmental programming and those being responsible for the positive effects of leptin are still unclear. It is possible, however, that maternal undernutrition results in hypoleptinemia during a critical period of development and that this reduction in leptin is the cue that initiates the programming cascade. Interestingly, it has been shown that leptin-deficient animals have reduced neural projections from the arcuate nucleus to a number of other hypothalamic nuclei involved in energy homeostasis. These projections can be normalized by exogenous leptin treatment but only if leptin is given during the neonatal period [5].

References

1. Flynn MAT, McNeil DA, Maloff B, Mutasinga D, Wu M, Ford C, Tough SC: Reducing obesity and related chronic disease risk in children and youth: a synthesis of evidence with 'best practice' recommendations. *Obes Rev* 2006;7(suppl 1): 7–66.
2. Speiser PW, Rudolf MC, Anhalt H, Camacho-Hubner C, Chiarelli F, Eliakim A, Freemark M, Gruters A, HersHKovitz E, Iughetti L, Krude H, Latzer Y, Lustig RH, Pescovitz OH, Pinhas-Hamiel O, Rogol AD, Shalitin S, Sultan C, Stein D, Vardi P, Werther GA, Zadik Z, Zuckerman-Levin N, Hochberg Z: Obesity consensus working group: childhood obesity. *J Clin Endocrinol Metab* 2005;90:1871–1887.
3. Wabitsch M, Denzer C, Grigem S, Fischer-Posovszky P: Obesity and weight regulation. Physiology and diseases; in Carel JC, Hochberg Z (eds): *Yearbook of Pediatric Endocrinology*. Paris, Elsevier, 2004, pp 173–184.
4. Wabitsch M: Prevention of obesity in young children; in *Encyclopedia on Early Childhood Development*. Centre of Excellence for Early Childhood Development. <http://www.excellence-earlychildhood.ca>

5. Bouret SG, Draper SJ, Simerly RB: Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science* 2004;304:108–110.
6. Wabitsch M, Hauner H, Heinze E, Muche R, Böckmann A, Partho W, et al: Body-fat distribution and changes in the atherogenic risk-factor profile in obese adolescent girls during weight reduction. *Am J Clin Nutr* 1994;60:54–60.
7. Wabitsch M: The acquisition of obesity: insights from cellular and genetic research. *Proc Nutr Soc* 2000;59:325–330.
8. Wabitsch M, Jensen PB, Blum WF, Christoffersen CT, Englaro P, Heinze E, Rascher W, Teller W, Tornqvist H, Hauner H: Insulin and cortisol promote leptin production in cultured human fat cells. *Diabetes* 1996;45:1435–1438.
9. Cederberg A, Gronning LM, Ahren B, Tasken K, Carlsson P, Enerback S: FOXO2 is a winged helix gene that counteracts obesity, hypertriglyceridemia, and diet-induced insulin resistance. *Cell* 2001;106:563–573.
10. Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M, et al: Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of IKK- β . *Science* 2001;293:1673–1677.
11. Kim JK, Fillmore JJ, Sunshine MJ, Albrecht B, Higashimori T, Kim DW, et al: PKC- θ knockout mice are protected from fat-induced insulin resistance. *J Clin Invest* 2004;114:823–827.
12. Medicherla S, Ma JY, Mangadu R, Jiang Y, Zhao JJ, Almiraz R, Kerr I, Stebbins EG, O'Young G, Kapoun AM, Luedtke G, Chakravarty S, Dugar S, Genant HK, Protter AA: A selective p38- α MAPK inhibitor reverses cartilage and bone destruction in mice with collagen-induced arthritis. *J Pharmacol Exp Ther* 2006, in press.
13. Reinehr T, Wabitsch M, Andler W, Beyer P, Böttner A, Chen-Stute A, Fromme C, Hampel O, Keller KM, Kilian U, Kolbe H, Lob-Corzilius T, Marg W, Mayer H, Mohnike K, Oepen J, Povel C, Richter B, Riedinger N, Schauerer G, Schmahfeldt G, Siegfried W, Smuda P, Stachow R, van Egmond-Fröhlich A, Weiten J, Wiegand S, Witte S, Zindel V, Holl RW: Medical care of obese children and adolescents. APV: a standardised multicentre documentation to study initial presentation and cardiovascular risk factors in patients transferred to specialised treatment institutions. *Eur J Pediatr* 2004;163:308–312.
14. Godoy-Matos A, Carraro L, Vieira A, Oliveira J, Guedes EP, Mattos L, Rangel C, Moreira RO, Coutinho W, Appolinario JC: Treatment of obese adolescents with sibutramine: a randomized, double-blind, controlled study. *J Clin Endocrinol Metab* 2005;90:1460–1465.
15. Chanoine JP, Hampl S, Jensen C, Boldrin M, Hauptman J: Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA* 2005;293:2873–2883.
16. Verdich C, Flint A, Gutzwiller JP, Naslund E, Beglinger C, Hellstrom PM, Long SJ, Morgan LM, Holst JJ, Astrup A: A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on ad libitum energy intake in humans. *J Clin Endocrinol Metab* 2001;86:4382–4389.
17. Druce MR, Small CJ, Bloom SR: Minireview: gut peptides regulating satiety. *Endocrinology* 2004;145:2660–2665.
18. Sun Y, Ahmed S, Smith RG: Deletion of ghrelin impairs neither growth nor appetite. *Mol Cell Biol* 2003;23:7973–7981.
19. Sun Y, Wang P, Zheng H, Smith RG: Ghrelin stimulation of growth hormone release and appetite is mediated through the growth hormone secretagogue receptor. *Proc Natl Acad Sci USA* 2004;101:4679–4684.
20. Wortley KE, Anderson KD, Garcia K, Murray JD, Malinova L, Liu R, Moncrieffe M, Thabet K, Cox HJ, Yancopoulos GD, Wiegand SJ, Sleeman MW: Genetic deletion of ghrelin does not decrease food intake but influences metabolic fuel preference. *Proc Natl Acad Sci USA* 2004;101:8227–8232.
21. Pantel J, Legendre M, Cabrol S, Hilal L, Hajaji Y, Morisset S, Nivot S, Vie-Luton MP, Grouselle D, de Kerdanet M, Kadiiri A, Epelbaum J, Le Bouc Y, Amselem S: Loss of constitutive activity of the growth hormone secretagogue receptor in familial short stature. *J Clin Invest* 2006;116:760–768.