Obesity and Weight Regulation

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The last 12 months have shown once more that obesity and weight regulation are among the most interesting biomedical fields of science. The number of high-quality papers reflects the multiple research activities which now can be documented at many places around the world. The last 12 months have also demonstrated that different governments in Europe have taken over some responsibility of the obesity epidemic as demonstrated by the European Charter on counteracting obesity (www.who.int). The aim of the Charter is to address the growing challenge posed by the epidemic of obesity on health, economies and development. The Charter has been established by the WHO European Ministerial Conference on Counteracting Obesity (Istanbul, Turkey, November 15–17, 2006). It acknowledges that the prevalence of obesity has risen up to threefold in the last two decades. Half of all adults and 1 in 5 children in the WHO European Region are overweight. Of these, one third is already obese, and numbers are increasing fast. Overweight and obesity contribute to a large proportion of non-communicable diseases, shortening life expectancy and adversely affecting the quality of life. More than 1 million deaths in the Region annually are due to diseases related to excess body weight. The trend is particularly alarming in children and adolescents, thus passing the epidemic into adulthood and creating a growing health burden for the next generation. The annual rate of increase in the prevalence of childhood obesity has been rising steadily and is currently up to ten times higher than it was in 1970. This Charter will also help scientists and physicians to stimulate experimental and clinical studies as well as preventive activities in their countries. This Charter should be known by every ESPE member.

For the yearbook selection this year, only articles published in journals with an impact factor of more than 4 were considered, assuming that relevant findings were published in these journals. The top findings of the last year lay within the areas of endocrinology of body weight regulation and endocrinology of the adipocyte. Two well-written reviews which are not included as an extensive summary are mentioned here:

Genetics of obesity in humans

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Endocr Rev 2006;27:710–718

In this review, human monogenic obesity syndromes with single gene defects that disrupt the molecules in the leptin-melanocortin pathway are reviewed. It is then shown how far the characterization of these patients has improved our understanding of the physiological role of leptin and the melanocortins in the regulation of human body weight and neuroendocrine function. The discovery of these genetic disorders has helped destigmatize human obesity and allow it to be seen as a medical condition rather than simply a moral failing. The genetic defects found to date all affect the drive to eat, resulting in hyperphagia in affected subjects. Thus, human food intake should not be considered as an entirely voluntarily controllable phenomenon, but rather one driven by powerful biological signals. It is likely that further discovery of causative genetic defects in humans and experimental animals will continue to highlight other molecular elements of the pathways involved in the regulation of body weight.

Emerging therapeutic strategies for obesity

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Medications approved so far to treat obesity promote no more than 5–7% loss of body weight, which is a drop in the ocean for the severely obese. New conceptual strategies are desperately needed. This

review provides an expanding list of molecular targets for novel, rationally designed anti-obesity pharmaceuticals. Many of the target molecules which we have described in earlier yearbooks [1–3] are included and open new hope for the development of better anti-obesity medications. Dieting and exercise remain the cornerstones of obesity therapy. However, more effective medicines to augment the impact of these efforts would be welcome among obese individuals as they fight against their energy homeostasis systems.

BMI z-score in children and risk factors

Increasing body mass index z-score is continuously associated with complications of overweight in children, even in the healthy weight range

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J Clin Endocrinol Metab 2007;92:517–522

Background: Most analyses of the complications of childhood overweight and obesity have categorized both child's weight (e.g. 'obese' or 'overweight') and the complications (e.g. 'presence' or 'absence') using arbitrary, percentile-based criteria. This study has the aim to show that BMI z-score is a continuous variable associated with risk factors and complications.

Methods: A total of 177 children were recruited from the community- and hospital-based arms of a larger growth and development study at the University of Western Australia. Children were recruited from the community through randomly selected primary schools. Overweight children seeking treatment were recruited through tertiary senders.

Results: Adjusted regression analysis showed that there was a linear relationship with BMI z-scores of systolic and diastolic blood pressure, fasting insulin, and ALT and a curvilinear relationship with insulin concentrations at 60 and 120 min of the oral glucose tolerance test, fasting C-peptide, HDL cholesterol and triglycerides, demonstrating a more unfavorable profile at the extremes of BMI z-score. In addition, musculoskeletal pain, obstructive sleep apnea symptoms, headaches, depression, anxiety, bullying, and acanthosis nigricans increased with child BMI z-score.

Conclusion: The z-score of the children was related to complications of overweight and obesity in a linear or curvilinear fashion, most complications increase across the entire range of BMI values and are not defined by thresholds.

This is one of the few studies showing that the risk of comorbidity in children is seen to increase continuously across the whole spectrum of childhood BMI z-scores, and is not limited to obese subjects. A child's BMI z-score is independently linearly or curvilinearly related to insulin resistance, liver enzymes and many medical complications. Interestingly, even in the so-called normal range of BMI this progression of risk factors is evident. These findings support recent recommendations of pediatric societies to screen children with an elevated BMI z-score for the occurrence of risk factors and complications. The threshold for such a screening might be lower than originally thought. In fact, this study tells us that all children, overweight or not, need to exercise and control their diet. Since the ethnical background is important for the occurrence of risk factors in association with increasing BMI z-scores in children, it is important that each country defines thresholds for such clinic programs on the basis of its own epidemiological data. The finding of this study will have implications for public health programs since it is obvious that decreasing the BMI of whole populations of children will decrease future disease burden.

Separation of human adipocytes by size: hypertrophic fat cells display distinct gene expression

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FASEB J 2006;20:1540–1542

Background: Adipocytes are known to release a variety of factors including cytokines, chemokines, and other biologically active molecules, commonly called adipokines. Obese individuals are known to exhibit elevated circulating levels of inflammation markers closely related to adipokines secreted in adipose tissue. A few studies have suggested that cytokine release within adipose tissue correlates with adipocyte size.

Methods: Adipocytes were isolated from subcutaneous adipose tissue samples. Separation of two adipocyte fractions with different size was achieved by several steps using suspension, washing, and filtrations. Microarray analysis of gene expression in small and large adipocytes was performed.

Results: 14 genes have been identified with a more than 4-fold expression in large cells as compared to small cells. Two of these genes were serum amyloid A (SAA) and transmembrane 4 L six family member 1 (TM4SF1) which were 19- and 22-fold higher expressed in large cells.

Conclusion: This study has identified genes with markedly higher expression in large, compared with small human adipocytes. These genes may link hypertrophic obesity to insulin resistance and type 2 diabetes.

Relationship between adipocyte size and adipokine expression and secretion

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J Clin Endocrin Metab 2007;92:1023–1033

Background: Adipocytes are known to release factors that may contribute to the proinflammatory state characteristic for obesity. The study was performed to get a better insight into possible underlying mechanisms investigating the effect of adipocyte size on adipokine production and secretion.

Methods: Adipose tissue was obtained from individuals undergoing elective plastic surgery. Isolated adipocytes were separated into four fractions (small, medium, large, and very large) by flotation. Adipokine release into medium was measured by highly sensitive sandwich ELISAs, and mRNA expression of adipokines was measured after RNA isolation from isolated cells.

Results: The secretion of the adipokines leptin, IL-6, IL-8, TNF- α , MCP-1, IP-10, MIP-1 β , G-CSF, IL-1ra, and adiponectin was positively correlated with the size of the adipocytes. After correction for cell surface, there was still a significant difference for leptin, IL-6, IL-8, MCP-1, and G-CSF between very large and small cells.

Conclusion: The fractionation of adipocytes according to cell size revealed that the very large adipocytes show a markedly impaired adipokine secretion which may promote inflammation in human adipose tissue.

The above-mentioned papers showed two simple methods for separating human adipocytes from adipose tissue samples into several populations according to their size. The findings in these two studies provide novel insight into the molecular connection between hypertrophic obesity and insulin resistance as well as type 2 diabetes. Obesity is characterized by an increase in fat cell number and fat cell size. Human fat cells can change 20-fold in diameter and several thousand-fold in volume. The hypertrophy of adipocytes in obese patients has been suggested to be critical for the occurrence of a chronic inflammatory state. Originally, Weisberg et al. [4] showed that with increasing adipocyte size the proportion of cells expressing CD68, a macrophage marker, increases in human adipose tissue. It has recently also been shown that adipocyte size correlates strongly with circulating

leptin levels [5–7]. In turn, weight loss results in a reduced adipocyte volume and a subsequent alteration in secretory activity, e.g. for leptin.

Adipocyte hypertrophy appears to cause a differentially impaired secretion between pro- and anti-inflammatory adipokines shifting the immunological balance towards the expression of proinflammatory proteins. It appears desirable to prevent adipocyte hypertrophy and/or to strive for a rapid removal of enlarged adipocytes.

The relationship between adipocyte size and macrophage accumulation suggests that hypertrophic adipocytes secrete factors that attract monocytes. The acute-phase protein serum amyloid A (SAA) is derived from hypertrophic adipocytes and may be involved in the process of attracting monocytes because SAA activates the chemotactic formyl peptide receptor like-1, which results in migration of blood monocytes and neutrophils [8, 9]. IL-8, also found to be expressed at high levels in hypertrophic adipocytes, may act as another potential monocyte recruiting factor in adipose tissue. Accumulation of macrophages in adipose tissue is likely to further increase the levels of inflammatory cytokines in adipose tissue and thereby increase insulin resistance [10].

Lipases: hormone-sensitive lipase is not the only one

Variation in the adiponutrin gene influences its expression and associates with obesity

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Background: Recent findings have identified three different proteins that seem to complement hormone-sensitive lipase (HSL), concerning triacylglycerol hydrolysis. One of these proteins is a membrane-associated protein called adiponutrin. The aim of the present study was to investigate the expression of adiponutrin in human obesity and its regulation in human adipocytes. Furthermore, it has been studied whether polymorphisms in the gene are associated with mRNA expression and function.

Results: Experiments in human adipocytes (SGBS cells) confirmed that the gene is upregulated in response to insulin in a glucose-dependent fashion. Adiponutrin mRNA expression levels are increased in obese subjects in subcutaneous and visceral adipose tissue. Two polymorphisms of adiponutrin have been identified showing an association with obesity. Carriers of these polymorphisms showed a lower adiponutrin mRNA expression and an increased basal lipolysis.

Conclusion: Genetic variation in adiponutrin is associated with obesity. The gene is upregulated in obese subjects. Its regulation is dependent on insulin and glucose. The results suggest that adiponutrin plays a so far unknown important role in the regulation of lipolysis and seems to be a candidate gene for obesity.

The release of energy from an adipocyte is controlled mostly by insulin, cortisol, growth hormone, and catecholamines, regulating the rate of lipolysis. So far, HSL has been believed to be the rate-limiting enzyme in the lipolytic process. Recently, three other proteins have been identified which participate in triacylglycerol hydrolysis at least under non-stimulated conditions. These proteins also exhibit transacylase activity in the catabolism of branched-chain amino acids [11–15].

The observation that HSL knockout mice retain a lean phenotype, residual lipase activity, and accumulation of diacylglycerol rather than triacylglycerol supports the hypothesis of the existence of complementary lipases.

Adiponutrin, which is identical to calcium-independent phospholipase A_{2c} , along with two other recently discovered lipases, desnutrin (identical to adipose triglyceride lipase or iPLA $_{2c}$) and GS-2 (identical to iPLA $_{2n}$), are prime candidates for this lipase activity.

The results of the present study show that adiponutrin is a candidate for an important player in the regulation of basal adipocyte lipolysis. The effect of carbohydrates on *adiponutrin* gene mRNA

expression is dependent on insulin. The relative contribution of this lipase requires however further investigations. In particular, the associations of obesity with two polymorphisms in adiponutrin should be viewed with caution until replicated in other populations.

Adipose tissue: reviews on new functions of the bodies energy store

Adipocytes as regulators of energy balance and glucose homeostasis

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Nature 2006;444:847–885

Role of adipose tissue as an inflammatory organ in human diseases

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Endocrine Reviews 2006;27:449–467

Adipose tissue: from lipid storage compartment to endocrine organ

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These three reviews are high-quality papers summarizing and interpreting recent findings on adipose tissue biology.

The review by Philip E. Scherer represents the Lilly lecture 2005. It summarizes findings on recently discovered adipokines and the secretory pathway of adipocytes. Furthermore, it shows the physiological impact of an acute loss of adipose tissue in relation to the consecutive lack of adipokines.

The review by Rosen and Spiegelman shows that adipose tissue serves as a crucial integrator of glucose homeostasis. It briefly examines the transcriptional basis of adipocyte development, and discusses energy homeostasis in mammals and how adipocytes regulate components of that system. The authors provide evidence that adipocytes have a crucial role in regulating glucose homeostasis through a series of endocrine and non-endocrine mechanisms. These involve adipose-derived secreted molecules, known as adipokines, neural connections and changes in whole-body physiology. Adipocytes have been a popular model for studying cell differentiation since the development of the murine adipose 3T3 cell culture system by Green and colleagues. Recently a human pre-adipocyte cell strain has been characterized with high capacity for adipocyte differentiation [16]. These cells now represent a unique model for studying human adipocyte differentiation and adipocyte biology, especially the regulation of adipokines. In the past decade, adipose tissue has moved from being a minor participant to having a central role in diverse homeostatic processes. These findings led to the idea that manipulation of adipocyte biology may be a useful therapeutic strategy in metabolic diseases, such as obesity and type 2 diabetes. Enhancement of leptin and adiponectin synthesis, and secretion and promotion of intra-adipocyte lipid oxidation are examples of approaches that might be expected to benefit patients.

Finally, the review by Schäffler et al. addresses the inflammatory role of adipose tissue outside the field of metabolism. In contrast to numerous and excellent publications describing the role of adipose tissue and adipokines in metabolism, reviews on the inflammatory role of adipose tissue outside this field are rare. The review summarizes and discusses the inflammatory role of adipocytokines and special types of regional adipocytes, such as retroorbital, synovial, visceral, subdermal, peritoneal,

and bone marrow adipocytes in different diseases, demonstrating another new and important role of the fat cell.

It remains to be seen how well we will translate these discoveries to our patients, but hopes for breakthrough therapies for obesity and diabetes are as high as they have ever been.

Central regulation of energy homeostasis – some new findings

Identification of nesfatin-1 as a satiety molecule in the hypothalamus

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Background: The brain hypothalamus contains certain secreted molecules that are important in regulating feeding behavior. Most of these molecules are also expressed in peripheral adipose tissue.

Methods: It was attempted to identify any new appetite-regulating molecule by using a subtraction-cloning assay of peroxisome proliferator-activated receptor- γ activator-stimulated genes in SQ-5 cells. The aim of the present study was to identify such new genes expressed in both brain medulloblastoma and 3T3-L1 adipocyte cells.

Results: Nine genes meeting these criteria were identified. Sequencing of the gene with the most profound stimulation by troglitazone demonstrated that it corresponds to a gene encoding DNA-binding/EF-hand/acidic protein (NEFA) or NUCB2. NUCB2 is composed of a signal peptide of 24 amino acids and a protein structure containing 396 amino acids. The homology of the amino-acid sequence of NUCB2 is highly conserved in humans, mice and rats. NUCB2 belongs to a homologous gene family together with nucleobindin1 (NUCB1). These two genes might have arisen from a single EF-hand ancestor and are so far of unknown function. NUCB2 is expressed in the appetite-control hypothalamic nuclei in rats. Nesfatin-1, an amino-terminal fragment derived from NUCB2, is present in cerebrospinal fluid and its expression is decreased under starvation. Injection of nesfatin-1 intracerebroventricularly decreases food intake in a dose-dependent manner. Conversion of NUCB2 to nesfatin-1 is necessary to induce feeding suppression. Nesfatin-1-induced anorexia in Zucker rats carrying a leptin-receptor mutation, and an anti-nesfatin-1 antibody, does not block leptin-induced anorexia. Furthermore, α -MSH elevates NUCB2 gene expression, and satiety by nesfatin-1 is abolished by an antagonist of the melanocortin-3/4 receptor.

Conclusion: This paper shows that nesfatin-1 is a newly discovered satiety molecule that is associated with melanocortin signalling in the hypothalamus.

This work has identified a novel anorexigenic molecule, nesfatin, derived from NUCB2 in the hypothalamus. NUCB2 is a prohormone that can be processed to generate bioactive fragments, such as nesfatin-1, located in the N-terminus of NUCB2. This molecule induces satiety. Nesfatin-1 might be a potential target for the development of drug therapies to treat obese persons.

There are complex but integrated interconnections among the hypothalamic nuclei in regulating feeding. Leptin and proopiomelanocortin (POMC)-derived α -MSH are key anorectic molecules in the hypothalamus. Studies in Zucker rats indicate a possible lack of involvement of hypothalamic leptin signalling in the induction of anorexia by nesfatin-1. In contrast, central injection of α -MSH stimulated the expression of NUCB2. Furthermore, an antagonist specific for the melanocortin-3/4 receptor abolished nesfatin-1-induced satiety. These findings show that hypothalamic nesfatin-1 signalling might involve a leptin-independent melanocortin signalling system.

Since nesfatin-1 might also be secreted by adipocytes it will be important to study its regulation and its possible involvement in the cross-talk between the energy stores of the body and the central regulatory system for energy balance.

Critical role for peptide YY in protein-mediated satiation and body-weight regulation

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Cell Metabolism 2006;4:223–233

Background: The satiating effect of dietary protein requires the gut-endocrine axis, since suppression of food intake is observed only when protein is administered enterally. It is not yet clear which hormones are involved in the transmission of this specific signal. Therefore, studies in normal and obese humans as well as in rodents were performed to investigate the effect of meal macronutrient composition on hunger scores and plasma concentrations of candidate hormones as there are PYY, ghrelin and GLP-1.

Results: In normal-weight and obese humans high-protein intake induced the greatest release of the anorectic hormone peptide YY (PYY) and the most pronounced satiety. When mice were fed with increased amounts of dietary protein, increased plasma PYY levels, decreased food intake, and reduced adiposity were found. In PYY null mice, protein had no satiating or weight-reducing effect, however treatment with exogenous PYY resulted in comparable effects as the high-protein diet in normal mice.

Conclusions: These results suggest that PYY is responsible for the satiating effect of dietary protein. Furthermore, it can be hypothesized that modulating the release of endogenous PYY through alteration of the diet could help to treat obesity more efficiently.

High-protein content meals have been shown to increase satiety and decrease food intake [17–19], resulting in both improved weight loss and weight loss maintenance [20–22]. Recently a number of gut-derived hormonal signals have been characterized [2]. PYY is produced by intestinal L-cells and is released into circulation after food intake. Circulating PYY3-36 inhibits appetite by acting directly on the arcuate nucleus via the Y2-receptor to which the hormone has a high affinity.

The present investigations aimed at understanding the effects of macronutrients on satiation and body weight in humans. They demonstrated that high-protein meals caused the greatest reduction in hunger coupled with the greatest increase in PYY. In the performed rodent studies, further support was generated for the hypothesis that PYY is a specific signal for the protein content of the diet. PYY null mice were resistant to the satiating effects of high-protein diets. In contrast, altering the fat and carbohydrate content of the diets while keeping the protein content constant resulted in a similar change in feeding, suggesting that deletion of PYY specifically affects the satiating effects of proteins. Further studies in humans are required to show that this specific effect of PYY can be critical for long-term body weight development.

Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor

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Background: So far only one mutation in the leptin-receptor gene (LEPR) has been reported. The 3 patients are characterized by severe early-onset obesity and very elevated serum leptin levels. The present study determined the prevalence of pathogenic mutations in the leptin receptor in a large cohort of patients with severe, early-onset obesity.

Methods: The leptin receptor was sequenced in 300 patients, characterized by severe obesity of early-onset (90 subjects out of a cohort from consanguineous families). Evaluation of metabolic, endocrine, and immune function in affected probands, relatives and controls was performed.

Results: Five nonsense and four missense mutations in 8 of the 300 patients were identified. The missense mutations resulted all in impaired receptor signalling. The phenotype of the affected subjects was characterized by hyperphagia, severe and early-onset obesity, delayed puberty, as well as alterations in the

immune function. Interestingly in these cases, serum leptin levels were within the range given for the elevated fat mass.

The mean BMI standard deviation score for the affected subjects was 5.1 ± 1.6 , as compared with 6.8 ± 2.1 for subjects with congenital leptin deficiency and 5.0 ± 1.5 for MC4R-deficient subjects.

Conclusions: In this cohort of patients with severe obesity the prevalence of pathogenic leptin-receptor mutations was about 3%. Therefore, congenital leptin-receptor deficiency should be considered in the differential diagnosis in any child with hyperphagia and severe obesity.

Although the prevalence of leptin-receptor mutations in this highly selected cohort is unlikely to reflect that in unrelated populations of obese subjects or in populations in which the age and the onset of obesity is more heterogeneous, the diagnosis of a pathogenic leptin-receptor mutation should be considered in children of early-onset extreme obesity, hyperphagia and eventually also in adolescents with extreme obesity and delayed puberty.

All frameshift mutations occurred in the N-terminal domain of the leptin receptor and were predicted to result in the loss of all leptin-receptor isoforms. The authors examined the functional properties of receptors with missense mutations and could show that in three of the missense mutations a complete loss of signalling (leptin-stimulated phosphorylation of STAT3) was found, whereas one missense mutation encodes a receptor with some residual ability to phosphorylate STAT3 in response to leptin.

The clinical phenotype of the affected patients was impressive: during an ad libitum test meal the probands with leptin-receptor mutations consumed almost three times the amount of energy that control subjects consumed. Interestingly, all 4 adults (all of them were female) had clinical evidence of hypogonadism, with a lack of pubertal growth spurt and reduced expression of secondary sexual characteristics; 3 had no menses until after 20 years of age. Furthermore, the children among them had more frequent childhood infections than did their siblings with wild-type leptin receptor. The premature deaths of 2 obese children in these families were associated with acute respiratory tract infections. It may be worth mentioning that leptin-deficient ob/ob mice exhibit several metabolic and immune abnormalities, including thymus atrophy and markedly reduced inflammatory responses, and that leptin normalized the metabolic, immune and inflammatory parameters in ob/ob mice.

Classically, patients with genetic obesity syndromes have been identified in childhood as a result of associated mental retardation and developmental abnormalities. In the present monogenetic disorders with leptin-receptor deficiency, obesity itself is the predominant presenting feature. This is comparable to cases with monogenetic disorders as leptin deficiency or melanocortin-4-receptor deficiency. These disorders result from disruption of the hypothalamic leptin-melanocortin signalling pathway. The described phenotypes of the subjects with leptin-receptor deficiency are comparable to the characteristic features of leptin deficiency including hyperphagia, obesity, hypogonadism, and impaired T-cell-mediated immunity.

The enemy is inside us – gut bacteria and weight gain

An obesity-associated gut microbiome with increased capacity for energy harvest

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Nature 2006;444:1027–1031

Background: The understanding of energy balance is the basis for the understanding of the development of obesity. The present article presents studies which determined if microbial community gene content correlates with and is a potential contributing factor to obesity in mice.

Methods: Distal gut microbiomes of ob/ob, ob/+ and +/+ littermates by random shot sequencing of their cecal microbial DNA were characterized. The predicted increased capacity for dietary energy harvest by the ob/ob microbiome was subsequently validated using biochemical assays and by transplantation of lean and obese cecal microbiotas into germ-free wild-type mouse recipients.

Results: Changes in relative abundance of two dominant bacterial divisions, the Bacteroidetes and the Firmicutes have been found in association with genetically obese mice (decreased ratio Bacteroidetes/Firmicutes) and their lean littermates (increased ratio Bacteroidetes/Firmicutes). Through metagenomic and biochemical analysis it has been shown that these changes affect the metabolic potential of the mouse gut microbiota. The microbiomes of obese mice have an increased capacity to harvest energy from the diet. Interestingly, this trait is transmissible and germ-free mice colonized with the microbiota show increases in their total body fat.

Conclusion: The results identified gut microbiota as an additional contributing factor to the pathophysiology of body weight regulation.

Human gut microbes associated with obesity

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Nature 2006;444:1022–1023

Background: Two groups of beneficial bacteria are dominant in the human gut, the Bacteroidetes and the Firmicutes. Earlier findings have proposed that the microbiota of obese individuals may be more efficient at extracting energy from a given diet than microbiota of lean individuals.

Methods: To investigate the relation between gut microbial ecology and body fat in humans, 12 obese people were studied on either a fat-restricted or a carbohydrate-restricted low-calorie diet. The composition of the gut microbiota was monitored over the course of 1 year by sequencing 16S ribosomal RNA genes from the stool samples.

Results: The relative proportion of Bacteroidetes is decreased in obese people when compared to lean people. The proportion of Bacteroidetes increases with weight loss on two types of low-calorie diet.

Conclusion: The findings indicate that obesity has a microbial component which might have potential therapeutic implications.

Much has been written about the sequencing of the human genome. However, our own genome is not the only one with which we need to be concerned. The human 'metagenome' is a composite of *Homo sapiens* genes and genes present in the genomes of the trillions of microbes that colonize our adult bodies. The latter genes are thought to outnumber the former by several orders of magnitude [23]. Our microbial genomes (the microbiome) encode metabolic capacities that have not evolved wholly on their own and remain largely unexplored. These include degradation of otherwise indigestible components of our diet, and therefore may have an impact on our energy balance.

The Firmicutes and the Bacteroidetes are divisions within the domain bacteria. The microbiota of the human gut is dominated by their members, most of which are benign. The Firmicutes is the largest bacterial phylum and contains more than 250 genera, including *Lactobacillus*, *Mycoplasma*, *Bacillus* and *Clostridium*. The Bacteroidetes include about 20 genera.

Colonization of adult germ-free mice with a distal gut microbial community harvested from conventionally raised mice produces a dramatic increase in body fat within 10–14 days, despite an associated decrease in food consumption. The change involves several linked mechanisms: microbial fermentation of dietary polysaccharides that cannot be digested by the host, subsequent intestinal absorption of monosaccharides and short-chain fatty acids, their conversion to more complex lipids in the liver and microbial regulation of host genes that promote deposition of the lipids in adipocytes.

The work described in the two articles raises the possibility that our gut bacteria is another factor that contributes to differences in body weight among individuals. The reports suggest that the differences in the efficiency of caloric extraction from food may be determined by the composition of the microbiota which in turn may contribute to differential body weights.

This is a potentially revolutionary idea that could change our views of what causes obesity and how we depend on the bacteria that inhabit our gut. However, many questions remain unanswered. Most notably, it is not clear whether such small changes in caloric extraction can actually contribute to the meaningful differences in body weight in humans. Furthermore, the questions about how and why the composition of gut microbiota is regulated will have to be answered. After these answers we are tempted to consider how we might manipulate the microbiotic environment to treat or prevent obesity.

The two papers open up an intriguing line of scientific inquiry that will allay microbiologists with nutritionists, physiologists and neuroscientists in the fight against obesity.

Obesity in Children and Adolescents: recent treatment trials

Randomised, controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin

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J Clin Endocrinol Metab 2006;9:2074–2080

Background: Insulin resistance associated with obesity in children and adolescents has become an increasing challenge in pediatric endocrinology. Metformin is a well-established, oral hypoglycemic agent in the treatment of adults with type 2 diabetes and other conditions with insulin resistance. The aim of the present study was to clarify the role of metformin therapy in pediatric patients with obesity.

Methods: 28 patients (13 males) aged 9–18 years were included in a crossover, randomized, controlled trial. The advantage of this kind of study design is that each patient acts as his own control, thereby minimizing inaccuracies in case-control matching and variability in adherence between patients on metformin vs. placebo.

Results: Metformin showed a significant treatment effect over placebo for weight (difference -4.35 kg), for body mass index (-1.26 kg/m²), for waist circumference (difference -2.8 cm). Subcutaneous abdominal adipose tissue (MRI) was also significantly reduced, whereas visceral abdominal adipose tissue was not differentially influenced by the treatment. Fasting insulin decreased more than in the placebo group (difference -2.2 mU/l).

Conclusion: The study demonstrates that metformin therapy for insulin resistance in obese children and adolescents is safe and well tolerated and has a beneficial effect on weight, BMI, waist circumference, subcutaneous abdominal fat, and fasting insulin.

The beneficial role of metformin in young patients with type 2 diabetes has been demonstrated in a randomized, controlled trial [24]. Metformin is also beneficial in pediatric patients with type 1 diabetes mellitus and insulin resistance [25–27]. There is also a positive treatment effect of metformin on girls with polycystic ovarian syndrome [28–31] and on children with non-alcoholic fatty liver disease [32]. The primary mechanism of action of metformin is by suppression of hepatic glucose production through activation of the insulin receptor, preferentially through insulin receptor substrate-2.

The effect on weight loss and insulin concentrations in obese children was first shown in a study by Lutjens and Smit [33]. Subsequent studies in children have shown that metformin is able to improve body mass index, fasting serum glucose, insulin, lipid profile.

In the present study a number of patients had also improved insulin sensitivity as measured by the minimal model, this however did not reach statistical significance. This might be due to the small number of patients and due to the fact that several patients underwent a change in their pubertal stage which is associated with a change in the physiological insulin resistance.

This double-blind, placebo-controlled, crossover trial increases our knowledge about effectiveness and safety of metformin (2×1 g/day) in children and adolescents with insulin resistance associated with obesity. The study results help to guide the clinician in the management of insulin resistance. The impact of metformin and any other drug tested so far was around 5% weight loss. There seems to be an inhibiting mechanism to surpass that magic number.

This study has to be taken in the right context: a very small cohort of obese children with questionable compliance to therapy. Several other studies, albeit less strict in their design, failed to show a positive metformin effect on either weight or insulin resistance.

The effect of sibutramine on energy expenditure and body composition in obese adolescents

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Background: Recently, two randomized controlled trials in obese adolescents were published, demonstrating the additional effect of sibutramine in a 6-month treating program comprising changing the daily diet and increasing daily physical activity. The present study was designed to evaluate the effect of sibutramine on body composition and energy expenditure in obese adolescents.

Methods: The trial was randomized, double-blind, placebo-controlled. It was a parallel-group trial of two treatment regimens. 24 obese adolescents (age 12–17 years) participated. The study was divided into two phases. The first phase included a randomized treatment period of 12 weeks, which included an energy-restricted diet, an exercise plan and either placebo or sibutramine 5 mg, taken once daily in the morning. After 2 weeks the dose was increased up to 10 mg daily. The second phase consisted of a follow-up period of 12 weeks with continuation of the diet and the exercise plan, however without the study medication.

Results: After intervention there were no significant differences between both groups in BMI-SDS, percentage fat mass, and total energy expenditure. During follow-up, BMI further decreased in the placebo group and stabilized in the sibutramine group. Interestingly, basal metabolic rate decreased in the placebo group and remained constant in the sibutramine group. During follow-up, basal metabolic rate decreased in the sibutramine group and increased in the placebo group.

Within the sibutramine group of the present study the changes in heart rate and blood pressure from baseline to intervention endpoint were not significant. However, abdominal complaints were scored significantly higher in the sibutramine group.

Conclusion: Sibutramine did not show to result in an additional decrease in BMI, BMI-SDS, or fat mass. Sibutramine seems to diminish the decrease in basal metabolic rate during weight loss in obese adolescents. Longer and larger trials may elucidate the place of sibutramine in the treatment of obese adolescents.

Sibutramine (β -phenethylamine) inhibits the re-uptake of noradrenaline and serotonin. It results in a reduced energy intake and stimulation of the sympathetic nervous system, leading also to an increased thermogenesis.

The current study investigated the effect of sibutramine on energy metabolism and body composition in obese adolescents. Two recent studies showed that over a short period of time, treatment of obese adolescents with sibutramine seems to be safe and results in significant weight losses [34, 35] – the magic 5%. Possibly due the strict lifestyle management which achieved beyond 5% weight loss, which is the first-line therapy for pediatric overweight, patients may have masked any potential effect of the study drug. Moreover, during follow-up the placebo group further decreased in BMI-SDS which could be interpreted as a rebound and adverse effect of sibutramine. However, the increase in BMI was mainly caused by an increase in fat mass.

The main new finding in this study is the possible effect of sibutramine on resting energy expenditure, illustrated by a stable basal metabolic rate during energy intake restriction. This study therefore does not support the use of sibutramine in the treatment of obese children and adolescents who participate in a lifestyle intervention program.

Review – Intake of sugar-sweetened beverages and weight gain: a systematic review

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This review tries to clarify the question if there is an association between the intake of sugar-sweetened beverages and weight gain by reviewing the English-language MEDLINE publications from 1966 to May 2005. Thirty publications (15 cross-sectional, 10 prospective, and 5 experimental) were selected on the basis of relevance and quality of design and methods. On the basis of the findings from large cross-sectional studies as well as well-powered prospective cohort studies with long periods of follow-up, it could be shown that there is a positive association between greater intakes of sugar-sweetened beverages and weight gain and obesity in both children and adults.

Intervention study

Effects of decreasing sugar-sweetened beverage consumption on body weight in adolescents: a randomised, controlled pilot study

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Background: The rapid increase in the consumption of sugar-sweetened beverages has occurred concomitantly with the escalating pediatric obesity epidemic. The American Academy of Pediatrics [36, 37] advocates reducing sugar-sweetened beverage consumption as a weight-control strategy based on available prospective data from cohort studies [38–40]. However, the available evidence for a causal relationship is inadequate to justify a change in the marketing practices. Therefore, the purpose of this study was to test the hypothesis that a simple environmental intervention will significantly decrease consumption of sugar-sweetened beverages and BMI among adolescents.

Methods: 103 adolescents between 13 and 18 years of age who regularly consumed sugar-sweetened beverages were included either in an intervention or in a control group. The intervention was performed for 25 weeks and relied largely on home deliveries of non-caloric beverages to displace sugar-sweetened beverages. The change in sugar-sweetened beverage consumption was the main process measure, and the change in body mass index was the primary endpoint.

Results: The consumption of sugar-sweetened beverages decreased in the intervention group by 82%. It did not change in the control group. In the intervention group, BMI changed by $0.07 \pm 0.14 \text{ kg/m}^2$ (mean $\pm$ SE) and in the control group by 0.21. This study has to be taken in the right context: a very small cohort of obese children with questionable compliance to therapy. Several other studies, albeit less strict in their design, failed to show a positive metformin effect on either weight or insulin resistance 0.15 kg/m^2 . The difference was not significant. However, among the subjects in the upper baseline BMI tertile, BMI change differed significantly between the intervention ($-0.63 \pm 0.23 \text{ kg/m}^2$) and control ($+0.12 \pm 0.26 \text{ kg/m}^2$) groups with a net effect of -0.75 . This study also has to be taken in the right context: a very small cohort of obese children with questionable compliance to therapy. Several other studies, albeit less strict in their design, failed to show a positive metformin effect on either weight or insulin resistance 0.34 kg/m^2 .

Conclusion: Decreasing the consumption of sugar-sweetened beverages seems to be a promising strategy for the prevention and treatment of overweight adolescents. Therefore, the results of this study support the guidelines of the American Academy of Pediatrics that recommend limiting sugar-sweetened beverage consumption.

Soft drinks are readily available in homes, fast food and other restaurants, vending machines, and school cafeterias. Those children and adolescents who consume soft drinks obtain 10–11% of their total energy intake from these beverages [41]. Several previous studies provide a physiological basis for a possible causal relationship between the consumption of sugar-sweetened beverages and weight gain. Sugar seems to be less satiating when provided in liquid compared with solid form, thus contributing to incomplete energy compensation [42, 43]. A beverage containing only sugar is less satiating than one with mixed nutrients while controlling for energy content and volume. The sugary beverage has also an attenuated thermogenic effect, indicating less nutrient oxidation and greater energy storage.

The present study follows the only pediatric trial so far by James et al. [44] in which a significant decrease in the incidence of obesity after 1 year among 7- to 11-year-old children was reported who received an intervention to decrease carbonated beverages compared with a control group. However, in this first study, baseline sugar-sweetened beverage consumption was very low and the decrease in consumption of all carbonated beverages for the intervention group was only 150 ml over 3 days with no significant change in sugar-sweetened beverage consumption. The present study is a more powerful intervention trial performed with adolescents who frequently consume sugar-sweetened beverages. A novel environmental intervention, in combination with telephone-administered behavioral counselling, to penetrate homes and thereby foster behavior change was used. This intervention led to a highly significant change in BMI of $-0.75 \pm 0.34 \text{ kg/m}^2$ in the intervention group compared with the control group among subjects in the upper baseline BMI tertile. This figure is by far better than any drug intervention reported so far.

From the data analysis it was calculated that BMI decreased on average by 0.26 kg/m^2 for every serving per day of sugar-sweetened beverage that was displaced. For comparative purposes, a prospective observational study found that BMI increased by 0.24 kg/m^2 for every additional serving of sugar-sweetened beverage consumed per day [38].

Although the present environmental intervention has been rather expensive (but not as expensive treating obesity-related complications), it should be relatively simple to translate it into a pragmatic public health approach. For example, schools could make non-caloric beverages available to students by purchasing large quantities at low costs. Assuming a unit price of 10 cents, an intervention designed to provide two servings of non-caloric beverages per day would cost approximately USD 35 per student over 25 weeks. This cost would compare favorably with that of other weight loss interventions for adolescents.

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