Obesity and Weight Regulation

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Once more, the recent literature on obesity and weight regulation demonstrates the activity and interest of this field of science. For the Yearbook selection this year, only articles published in journals with a high impact factor were considered, assuming that relevant findings were published in these journals.

The highlights are papers about the further functional characterization of the fat mass- and obesity-associated (FTO) gene, about strong evidence of a continuous turnover of adipocytes in white adipose tissue, about brown adipose tissue in man as a target for the regulation of homeostasis, and about factors influencing weight maintenance after weight loss therapy. Furthermore, evidence-based recommendations on prevention and treatment of obesity in children and adolescents are now available.

New insights into the function of fat mass-and obesity-associated (FTO) gene

Fat mass-and obesity-associated (FTO) gene variant is associated with obesity: longitudinal analyses in two cohort studies and functional test

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Background: A huge number of polymorphisms influencing weight and BMI have been identified. The best reproducible association exists for variants in the FTO gene. So far however, little is known about the function of FTO, its influence on metabolism and time-related changes in the influence on BMI.

Methods: 2,287 men and 3,520 women from two prospective cohorts (Nurses' Health Study and Health Professional Follow-Up Study) were genotyped for the common variant rs9939609. Plasma adiponectin and leptin were measured in a subset of diabetic men (n=854) and women (n=987). Expression of FTO was tested in adipocytes from mice lacking the leptin-receptor (db/db mice) and in wild-type mouse macrophages.

Results: Rs9939609 was associated with increased BMI and risk for overweight/obesity in men and women both in young adulthood and later in life. The association between this polymorphism and obesity risk showed a tendency to decline with increasing age in men.

Heterozygosity and homozygosity for the risk allele were associated with type 2 diabetes in both men and women and with lower adiponectin and higher leptin levels in women. However, these associations became non-significant when adjusted for BMI.

FTO was expressed in several metabolically active tissues in humans and wild-type C56BL/6 mice. In db/db mice FTO expression in white adipocytes was reduced by 50%.

Conclusion: The study confirms an association between a common FTO variant and BMI over a wide age-range. Observed connections between this variant and diabetes-risk or changes in adipocytokine levels were mediated via BMI. Db/db mice showed a decreased expression in FTO.

Increasing heritability of BMI and stronger associations with the FTO gene over childhood

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Background: Twin research has been pivotal in identifying the substantial genetic impact on individual differences in BMI. A huge number of polymorphisms influencing weight and BMI have been identified; with the best reproducible association for variants in the FTO gene. However, the magnitude of genetic influence on BMI seems to change with age. Up to date very few longitudinal twin analysis have been performed to assess this age-dependency.

Methods: Repeated BMI assessments at 4, 7, 10 and 11 years of age were performed in a longitudinal sample of >7000 children from the Twins Early Development Study in the United Kingdom. Analyses for the FTO polymorphism rs9939609 were conducted in one member of each pair, for which DNA material was available (around 2800 children).

Results: The differences between monozygotic and dizygotic twins in twin-correlation for BMI increased from age 4 to age 11 whereas shared environmental influence decreased. The association between the FTO variant and BMI rose in parallel to the gain in heritability, going from $R^2 < 0.001$ at age 4 to $R^2 = 0.01$ at age 11.

Conclusion: The findings suggest that either expression of FTO becomes stronger throughout childhood or that children increasingly select an environment suiting their genetic propensities.

Both articles address the important issue of the mechanisms underlying the influence of genes on BMI. Variants in the FTO gene are well established among the potential factors [1–3], different population studies yield wildly differing results concerning the magnitude of this influence. At least in part this might be attributable to different age ranges in the groups examined. Although longitudinal studies avoid some of the confounding factors identified in cross-sectional studies, few studies longitudinal studies on the influence of gene variants on BMI exist. In the first article long-term changes in two large general populations are examined. In the second the more specific aspects of longitudinal twin studies are used. The twin study shows a clear age-dependency with an increased influence of age. According to the population study this influence might wane in later years, however, these changes were non-significant. These articles highlight the complexity of gene/environment interactions and add yet another puzzle piece to our understanding.

Inactivation of the FTO gene protects from obesity

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Background: Recently, a strong correlation between polymorphisms in the human FTO gene and body mass index was identified by several independent genome-wide association studies. Common risk variants in the first intron of this gene define a risk allele predisposing to obesity. Homozygous carriers of the risk allele were on average ~3 kg heavier and had a 1.67-fold increased risk of obesity than control persons. However, the functional impact of FTO in energy homeostasis remains elusive.

Methods: *Fto*^{-/-} mice were generated by replacement of exons 2 and 3 of the *Fto* gene by a neomycin resistance cassette. The deletion success was verified by western blot and qRT-PCR analysis in different tissues. Given the suggested function of FTO in energy metabolism, *Fto*^{-/-} mice and controls were analysed concerning their body composition, energy homeostasis and physical activity.

Results: The deletion of *Fto* in mice leads to a growth retardation 2 days after birth onwards and a reduction in lean and fat mass, despite decreased physical activity and relative hyperphagia. This leanless develops as a consequence of increased energy expenditure and systemic sympathetic activation.

Conclusion: This study provides data that *Fto* is a functional mediator of energy homeostasis by the control of energy expenditure.

This study provides functional data about the role of *Fto* (fat mass and obesity associated) in energy metabolism of mice. This is important since its functional relevance in metabolism is unclear. Common

gene variants in the first intron of this gene have recently been found by genome wide analyses to be associated with traits of obesity. Fischer et al. generated mice lacking this gene and compared them with wildtype and heterozygous (*Fto*^{+/-}) mice. *Fto*^{-/-} mice did not differ in body weight during embryonic development, but growth retardation became apparent at postnatal day 2 and remains stable throughout the entire lifespan of these mice. After six weeks, the body weight between homozygous and wt mice differed by approximately 30–40%, whereas heterozygous mice did not show any significant weight reduction. This reduction in weight was associated with a significant loss of white adipose tissue, with nearly complete loss after 15 months. Interestingly, this reduction in weight and fat was not due to a lower food intake of the mutants. In fact, these mice ate more in proportion to their body weight compared to wildtype animals. Moreover, both groups of mutant mice gained less weight on a high fat diet. Instead, *Fto*^{-/-} mice show an increased energy expenditure, while their physical activity was decreased. The authors conclude that the increase in energy expenditure was due to a higher activity of the sympathetic system, shown by enhanced levels of adrenaline and noradrenaline. The authors suggest that *FTO* risk alleles might lead to an altered expression of *FTO* resulting in a higher individual susceptibility to obesity. It would be interesting to identify the molecular pathways by which *FTO* influences the sympathetic system. Additionally, tissue-specific knock-outs in areas which are relevant to energy homeostasis and metabolism are needed. The sympathetic system might turn out as a substantial mediator for the action of *FTO*.

Adipose tissue revisited

Strong evidence for fat cell turnover in white adipose tissue: target for pharmaceutical intervention?

Dynamics of fat cell turnover in humans

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Nature 2008;453:783–787

Background: Obesity together with its enhanced risk of cardiovascular diseases and metabolic disorders like type 2 diabetes is increasing in an epidemic manner. The size of the adipose tissue mass is determined by the number of fat cells as well as their volume. The increased lipid storage in already existing adipocytes is thought to be the most important mechanism by which the fat mass expands during obesity.

Methods: The authors combined previously observed data concerning the number of adipocytes in children and adolescents with data about the number of adipocytes from lean and obese adults before and after a major weight loss. Additionally, they measured the adipocyte turnover rate in lean and obese adults by analyzing the integration of atmospheric ¹⁴C derived from nuclear bomb tests during the cold war into the genomic DNA of fat cells via accelerator mass spectrometry.

Results: The major results of this paper are that the number of adipocytes is set during childhood and shows only slight variations during adulthood. Even after a significant weight loss the authors could only detect a decreased adipocyte volume but no changes in the number of adipocytes. They observed, however, a remarkable turnover rate of the adipocytes. Approximately 10% of fat cells were renewed annually at all adult ages and levels of body fat index. Neither death rate nor the generation of new adipocytes was altered in early onset obesity, suggesting a tight regulation of fat cell number in this condition during adulthood.

Conclusion: The high adipocyte turnover offers a new target towards pharmacological therapy of obesity and it will be important to identify the molecular feedback mechanisms controlling adipocyte turnover.

To date the knowledge about adipocyte cell turnover in humans is very restricted. In animal experiments incorporation of labelled nucleotides can be used to study cell turnover but due to its poten-

tial toxicity it is not possible to perform this method in humans. In this study, the authors came up with a clever solution by utilizing the rapid increase in atmospheric ^{14}C levels which resulted from nuclear bomb tests during 1955–1963. In 1963 the ban of these nuclear tests resulted in a drop in atmospheric ^{14}C to the levels before the cold war. Once the ^{14}C is integrated into the genomic DNA of an adipocyte, it remains until the cell dies and degrades its DNA. Monitoring ^{14}C incorporation, the authors were able to date the generation of the adipocytes in adipose tissue of humans who grew up during the time of decreasing atmospheric ^{14}C levels.

It was previously shown that obesity is associated with an increased infiltration of macrophages into the adipose tissue which indicates an elevated death rate of adipocytes [7]. In contrast, Spalding et al. could not observe differences between cell death rates in lean and obese patients. One explanation may be the small sample size of 13 lean and 14 obese subjects. However, there is a trend toward increased death rate and decreased age of the adipocytes in obese subjects. The finding that there is a pool of early committed white adipocyte precursors in the mural cell compartment of the adipose vasculature [8] supports the idea of a constant turnover of adipocytes during lifespan and supplies a putative source for the new adipocytes. Thus, unlike previous contention, new fat cells are continually being born to replace their dead predecessors. The average age of a fat cell seems to be about 10 years in both lean and obese individuals, and the number of fat cells as a proportion of all cells remains constant in each weight group. But the total number of new fat cells was higher in obese subjects, suggesting that they are replenishing an existing larger pool. In summary, this paper offers a new possible pharmacological target for treating obesity, therefore emphasizing the high impact of research on the molecular mechanisms underlying this adipocyte turnover.

White fat progenitor cells reside in the adipose vasculature

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Science 2008;322:583–586

Background: Adipocytes form throughout life, with the most marked expansion of the lineage occurring during the postnatal period. Endogenous adipocyte progenitors probably reside in the adipose stromal-vascular fraction (SVF), a heterogeneous mixture of cells. Peroxisome proliferator-activated receptor γ (PPAR γ), a central regulator of fat formation, is necessary and sufficient for adipogenesis. Thus, marking PPAR γ -expressing cells *in vivo* might provide insight into adipose lineage specification.

Methods: The authors generated PPAR γ -reporter strains to isolate proliferating and renewing adipogenic progenitors. PPAR γ -GFP-positive cells were localized to the vasculature, and their adipogenic potential was observed.

Results: The SV compartment of adipose depots contained PPAR γ -expressing cells which behaved as an amplifying population and contributed to the adipocyte lineage. These progenitors were already committed, either prenatally or early in postnatal life and resided in the mural cell compartment of the adipose vasculature, but not in the vasculature of other tissues. They were phenotypically distinct from adipocytes and other SV cells and had a unique molecular signature. The precursors were adipogenic and also expressed mural cell markers.

Conclusion: A population of early committed white adipocyte precursors appears to be mural cells that reside in the vasculature of adipose tissue. Thus, the adipose vasculature might function as a progenitor niche providing signals for adipocyte development.

Although adipocytes are postmitotic, white adipose tissue mass retains the ability to expand throughout adult life by an increase in adipocyte number [9]. Recent studies suggest that approximately 10% of the body's fat cells are regenerated each year [10]. Nevertheless, there is only limited knowledge on the identity and localization of adipocyte precursors *in vivo*. In the present publication, Tang et al. identified an adipogenic cell population expressing both PPAR γ and mural markers. These proliferating progenitors were committed either prenatally or early in life and resided in the mural cell compartment of adipose vasculature. The authors conclude that the adipose vasculature appears to function as a progenitor niche and may provide signals for adipocyte development. Their data support the previous finding of preadipocytes existing in the adipose vasculature [11] and contradict the classical idea that adipocyte formation occurs later during development.

Adipose tissue revisited

Brown adipose tissue as a natural target for modulating energy expenditure in man

Identification and importance of brown adipose tissue in adult humans

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N Engl J Med 2009;360:1509–1517

Background: While brown adipose tissue (BAT) is known to regulate energy expenditure in rodents, it was regarded to have no physiologic relevance in adult humans.

Methods: 1,972 patients were analyzed by ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron-emission tomographic and computed tomographic (PET-CT) scans in order to identify BAT. PET-CT data were related to clinical data. UCP-1 immunohistochemistry was performed on biopsy specimens from putative BAT depots.

Results: By PET-CT, remarkable depots of BATe depots were identified in regions from the neck to the thorax. Females had a 2-fold higher mass of BAT and higher ^{18}F -FDG uptake activity. BAT was inversely correlated to body mass index.

Conclusion: Substantial amounts of BAT were identified in adult humans. An inverse correlation of the amount of BAT with BMI suggests a potential role of BAT in human metabolism.

Functional brown adipose tissue in healthy adults

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N Engl J Med 2009;360:1518–1525

Background: While BAT helps maintain normal body temperature in newborn infants, it was considered to have no physiologic relevance in adults.

Methods: 5 healthy subjects underwent ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron-emission tomographic and computed tomographic (PET-CT) scans during cold exposure or during warm temperature. BAT tissue samples were subjected to immunohistochemistry and quantitative RT-PCR using primers specific for BAT marker genes.

Results: Cold-induced glucose uptake was increased by a factor of 15 in supraclavicular BAT in all 5 patients compared to an increase by a factor of 4 in white adipose tissue. Expression of BAT markers such as UCP-1 and DIO2 (deiodonase, iodothyronine, type 2) was demonstrated in BAT specimens.

Conclusion: BAT is present in adult humans.

Cold-activated brown adipose tissue in healthy men

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N Engl J Med 2009;360:1500–1508

Background: Studies in animals indicate that BAT is important for the regulation of body weight.

Methods: 24 healthy men (10 lean, BMI <25, and 14 overweight, BMI >25) were studied under thermoneutral conditions (22°C) or during mild cold exposure (16°C). BAT was determined by ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron-emission tomographic and computed tomographic (PET-CT) scan. Body composition and energy expenditure were measured by dual-energy X-ray absorptiometry and indirect calorimetry.

Results: During cold exposure, BAT activity was found in 23 subjects. The activity was lower in overweight compared to lean subjects. The percent of body fat and BMI were negatively correlated with BAT, while the resting metabolic rate had a positive correlation.

Conclusion: BAT is present in adult humans. Its activity is reduced with overweight or obesity.

^{18}F -FDG PET-CT measures uptake of ^{18}F -labelled deoxyglucose into metabolically active tissues and is usually used in the diagnosis of neoplasms and their metastases. PET-CT radiologists knew of a bizarre dark knots and stripes along the neck and paraspinally that occur more frequently when their patients were exposed to excessive air-conditioning, but we only now understand that these represent BAT. The 3 above-mentioned studies used this method to identify metabolically highly active BAT depots.

The common message from these studies is that BAT is present and active in adult humans, and its presence and activity are inversely associated with obesity and indexes of the metabolic syndrome. The major shortcoming of these studies is the lack of a direct correlation between cold-stimulated changes in energy expenditure and BAT activity. This could be secondary to the inability of the PET-CT technique to measure the activity of small nests of BAT.

However, these studies point to a potential 'natural' intervention to trigger energy expenditure by turning down the heat and burning calories.

This conclusion is certainly an oversimplification. Nonetheless, BAT provides a target for pharmacologic and environmental interventions, aimed at modulating energy expenditure.

A new weapon in the fight against obesity and diabetes: SIRT1 activation

Specific SIRT1 activation mimics low energy levels and protects against diet-induced metabolic disorders by enhancing fat oxidation

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Background: The NAD⁺-dependent deacetylase SIRT1 controls metabolic processes in response to low nutrient availability. New, selective activators of Sirt1 such as SRT1720 are currently tested for suitability as therapeutic agents for the treatment of metabolic disorders.

Methods: Male 7-week-old C57BL/6J mice were fed a standard or HF diet supplemented or not with SRT1720. Animals were phenotyped in terms of body weight, food intake, muscle, liver and adipose tissue function.

Results: SRT1720 administration robustly enhances endurance running performance and strongly protects from diet-induced obesity and insulin resistance by enhancing oxidative metabolism in skeletal muscle, liver, and brown adipose tissue. These metabolic effects of SRT1720 are mediated by the induction of a genetic network controlling fatty acid oxidation through a multifaceted mechanism that involves direct deacetylation of PGC-1 α , FOXO1, and p53 and the indirect stimulation of AMPK signaling through a global metabolic adaptation mimicking low energy levels.

Conclusion: This study further validates SIRT1 as a target for the treatment of metabolic disorders and characterizes the mechanisms underlying the therapeutic potential of SIRT1 activation.

Calorie restriction has been shown to delay age-related diseases and to extend lifespan in numerous species including mammals. It has long been assumed that the extension of life span by calorie restriction is mediated in a passive way by lowering oxidative stress, DNA damage and apoptosis. Ongoing studies now show that the response to calorie restriction is a highly regulated process and SIRT1 has been identified as the key molecular player. One natural activator of Sirt1, the polyphenolic substance resveratrol, is found in grapes and red wine. Resveratrol came to our attention because it was linked to the so-called French paradox, which describes the fact that French people have a lower risk of developing cardiovascular disease compared to other Europeans. This finding was linked to the moderate consumption of red wine and to the substance resveratrol. Resveratrol has since been shown to limit diet-induced obesity, to increase energy efficiency and to prevent diabetes in mice. Since resveratrol exerts versatile functions by activating several intracellular pathways, researchers have now developed small molecule drugs which are much more potent than resveratrol and specifically target Sirt1.

Preclinical studies with SIRT1 activators have demonstrated potential importance in multiple disease areas, including type 2 diabetes and related complications, mitochondrial disorders, cardiovascular disease, inflammation, neurodegenerative diseases, and cancer. Early clinical studies have demonstrated promising results in type 2 diabetes.

Weight loss maintenance – an everlasting challenge

Lifestyle intervention in obese children with variations in the melanocortin 4 receptor gene

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Background: The melanocortin 4 receptor (MC4R) is a critical regulator of energy homeostasis in men and mutations in the MC4R gene leading to reduced receptor function are assumed to have a major effect on body weight. Although functionally relevant mutations in the MC4R gene are reported to have a considerable prevalence in obese children and adolescents, little is known about the impact of these mutations on the effect of a lifestyle intervention program.

Methods: A cohort of 514 overweight children aged 5–16 years participating in a 1-year multidisciplinary lifestyle intervention program was screened for mutations in the MC4R gene. Children carrying a MC4R mutation leading to reduced receptor function (group A) were each matched with 5 subjects without MC4R mutations (group B). All study participants underwent comprehensive metabolic phenotyping.

Results: 16 children (3.1%) were identified with nonsynonymous mutations leading to reduced receptor function and 17 children (2.7%) with MC4R variations not leading to reduced receptor function. Nine of the total of 16 children of group A (56%) and 46 of the 80 children of group B (58%) started the intervention. Furthermore, 1 subject in group A and 5 subjects in group B dropped out of the intervention program. BMI z-score was reduced in both groups to a similar degree at the end of the 1-year intervention. In contrast, only children without MC4R mutations (group B) maintained the weight loss over a 1-year post-intervention follow-up period, whereas BMI z-score in carriers of MC4R mutations (group A) did not differ significantly from baseline after follow-up (intention to treat analysis). Children in groups A and B did not differ with regard to anthropometrical markers, hormone profile, or cardiovascular risk factors.

Conclusion: The study demonstrates that children affected by MC4R mutations can lose weight by multidisciplinary lifestyle intervention but seem to have difficulties in maintaining weight loss over short-term follow-up.

Since the cloning of the fourth member of the melanocortin receptor family [12] and the first descriptions of the clinical phenotype of severe obesity associated with mutations in its gene [13, 14], MC4R mutations have become one of the best investigated genetic causes of obesity. Reported prevalence rates of up to 5.8% for MC4R deficiency make these mutations potentially the most common form of monogenic obesity in humans. Even the existence of a 'MC4R syndrome' characterized amongst others by early onset obesity, increased linear growth, hyperphagia, and pronounced hyperinsulinemia has been proposed [15]. In their present study, Reinehr et al. add to the field of MC4R research important information on the impact of reduced MC4R function on the chances of success of an outpatient weight management program for affected individuals. En passant four novel MC4R mutations were identified and functionally characterized. The present study demonstrates that carriers of MC4R mutations can achieve significant weight loss under the conditions of an intensive outpatient lifestyle intervention program, but only 1 year after the end of intervention there was no detectable change of BMI z-score in the MC4R group compared to baseline, while non-mutated children sustained their degree of weight loss. Furthermore, Reinehr et al. were unable to identify clinical or

laboratory markers pointing to MC4R mutations, therefore questioning – as do other authors – the idea of a ‘MC4R syndrome’. In summary, the present study provides further data on the impact of MC4R mutations on weight status, and advocates MC4R mutation screening at least in obese children and adolescents with a strong family history of obesity, obese siblings or rapid weight gain after obesity interventions. Nonetheless, the key question of how to treat patients with a strong genetic predisposition for obesity remains unanswered.

Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli

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J Clin Invest 2008;118:2583–2591

Background: Increased hunger and food intake during diet are critical problems in the clinical management of obesity. Therefore, physiological changes in neuronal activity regulating energy intake and expenditure during starvation/diet are of special interest.

Methods: Brain-region specific neural activity was examined by functional MRI in 6 obese subjects. Responses to food-related visual cues were assessed during states of normal weight and after stabilization at a 10% reduced body weight, while the patients received either injections of leptin or placebo.

Results: Weight loss-elicited changes in neural activity were partly reversible by leptin treatment. Specifically, weight loss-induced increases in neural activity-response in the brainstem, culmen, parahippocampal gyrus, inferior and middle frontal gyri, middle temporal gyrus and lingual gyrus were reversed by leptin, as were decreases in activity in the hypothalamus, cingulate gyrus and middle frontal gyrus.

Conclusion: Weight loss elicits changes in neuronal activity in areas known to be involved in the regulatory, emotional, and cognitive control of food intake. These changes were partly reversible by leptin, indicating that leptin levels might play an important role in increased feelings of hunger during diet.

The discovery of the anorectic hormone leptin [16] provoked an enthusiastic response worldwide in the hope of finally having found a medical treatment for obesity. The subsequent realization that obesity as such represents a state of leptin resistance and that leptin treatment seems to be effective only in rare states of leptin deficiency [17] was disillusioning. During diet, leptin levels are decreased and Rosenbaum et al. have shown before that restoration of leptin levels to pre-weight loss levels reverses several metabolic and behavioral changes induced by diet [18]. In this article they now show elegantly that this reversal in behavioral changes has a correlation with changes in neuronal activity, thereby highlighting the importance of specific brain areas in regulating energy homeostasis mediated by leptin. These findings overlap at least in part with changes seen by Farooqi et al. [19] in leptin-deficient children before and after treatment with leptin.

New mechanism

Intestinal gluconeogenesis is a key factor for early metabolic changes after gastric bypass but not after gastric lap-band in mice

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Background: Gastric bypass surgery also has immediate metabolic benefits that precede any substantial weight loss. The aim of the present study was to compare early metabolic changes after gastric bypass versus gastric lap-band (GLB) in mice.

Methods: Energy and glucose metabolism following two experimental bariatric surgical procedures were compared to sham-operated high-fat diet-induced obese C57Bl6 and RIPGLUT1 × GLUT2^{-/-} mice. In the first procedure a restrictive GLB was positioned around the upper stomach to create a small proximal and large distal gastric pouch. Alternatively, the pyloric sphincter was ligatured, followed by an enterogastric anastomosis (EGA) allowing a bypass of the duodenum and proximal jejunum as a surrogate for Roux-en-Y gastric bypass (RYGB). Food intake, body weight and composition as well as metabolic effects of bariatric surgery in mice were assessed.

Results: Food intake was significantly decreased in EGA mice, while the body fat loss was similar compared to sham-control and GLB mice. In addition, insulin sensitivity and intestinal gluconeogenesis increased after the EGA procedure independent of the GLP-1 action, but not after gastric banding (GLB). All EGA effects could be blocked in GLUT-2 knockout mice and in mice with portal vein denervation.

Conclusion: This study provides evidence that the beneficial effects of the EGA procedure on food intake and glucose homeostasis involve intestinal gluconeogenesis and its detection via a GLUT-2 and hepato-portal sensor pathway.

Bariatric bypass surgery is an increasingly popular treatment option for obese patients, and adolescents are being operated more frequently than ever before. It has traditionally been assumed that bariatric operations cause weight loss through gastric restriction, intestinal malabsorption, or both. Long-term total mortality especially from diabetes, heart disease and cancer was significantly reduced after gastric bypass surgery. Unexpectedly, the typical RYGB procedure seems to have the potential to also reduce type 2 diabetes mellitus even in patients without obesity. Although there is growing interest in using RYGB, the mechanisms mediating the metabolic effects of this procedure remain poorly understood. Potential mechanisms underlying the direct anti-diabetes effects of RYGB include enhanced nutrient stimulation of lower intestinal hormones (e.g. glucagon-like peptide-1), altered physiology from excluding ingested nutrients from the upper intestine, compromised ghrelin secretion, modulation of intestinal nutrient sensing and regulation of insulin sensitivity. The mechanistic model by Troy et al. using a gastric bypass model in mice proposes that glucose produced by defined intestinal segments is secreted directly into the portal vein where changes in blood glucose are detected by sensory fibers presumably projecting to central nervous system circuits controlling food intake, insulin secretion and nutrient partitioning. Elucidating the physiologic mechanisms underlying these surgical procedures should be an important research priority and might lead to new pharmaceuticals that would obviate the need for surgery.

Food for thought

Adenotonsillectomy and the development of overweight

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Background: Although some studies have shown that after adenotonsillectomy in childhood weight gain was accelerated, this finding has not been considered as a risk factor for overweight and obesity in children yet. The aim of this study was to investigate the association between adenotonsillectomy and the subsequent development of overweight in the general population.

Methods: The study sample included 3,963 children enrolled in the Dutch Prevention and Incidence of Asthma and Mite Allergy birth cohort. Annual questionnaires completed by the parents provided data on weight and height as well as on covariate factors known to influence weight development. Weight and height at 8 years of age has been measured.

Results: Undergoing adenotonsillectomy from birth to age 7 was significantly associated with overweight and obesity at 8 years of age. Being overweight at 2 years of age did not predict an increased risk of adenotonsillectomy at older ages.

Conclusion: These longitudinal data on weight and height in the years before and after surgery suggest that adenotonsillectomy form a turning point between a period of growth faltering and a period of catch-up growth, which might explain the increased risk of developing overweight after the operation.

Limitations of this study include loss to follow-up for the medical examination where weight and height were measured and that most data were parentally reported.

The cumulative incidence of adenotonsillectomy up to age 8 years was 12%, for adenotonsillectomy it was 15%. These numbers are rather high compared to the incidences in other countries.

Children who underwent the operation had a higher prevalence of low maternal education, maternal overweight, smoking, and no breastfeeding. After controlling for these factors, the authors concluded that operations were independently associated with the risk for overweight and obesity at age 8 years.

Growth and growth biomarker changes after adenotonsillectomy: systematic review and meta-analysis

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Arch Dis Child 2009;94:83–91

Background: It is well established that sleep disordered breathing in children secondary to adenotonsillar hypertrophy is a risk factor for growth failure. Adenotonsillectomy itself is associated with increases in height, IGF-1 and/or IGFBP-3 and interestingly also in weight. So far only small cohorts including less than 100 children were not able to strengthen the hypothesis of a causal relationship.

Methods: This is a systematic review and meta-analysis including studies from 1980 to 2007 for anthropometrics, the meta-analysis included studies presenting z scores or percentiles.

Results: Twenty of 211 studies met the review criteria. The meta-analysis found significant increases in weight and height z-scores, and IGF-1 and IGFBP-3 serum levels after adenotonsillectomy.

Conclusion: The findings suggest that primary care providers and specialists should consider sleep disordered breathing secondary to adenotonsillar hypertrophy when screening, treating and referring children with growth failure. Adenotonsillectomy might be followed by excessive weight gain and the development of overweight.

It is established that sleep disordered breathing which is characterized by snoring, mouth breathing and obstructive sleep apnea, is a risk factor for growth failure. Adenotonsillar hypertrophy is the primary factor associated with sleep disordered breathing in children.

Several possible mechanisms might explain a relationship between sleep disordered breathing and growth failure. Sleep disordered breathing interrupts slow-wave sleep, when growth hormone is preferentially secreted. Impaired growth hormone secretion results in decreased IGF-1 and/or IGFBP-3 levels. Sleep disordered breathing can also lead to growth failure by the associated increases energy expenditure during sleep and the reduced appetite induced by pharyngeal dysphagia associated with adenotonsillar hypertrophy. Sleep disordered breathing is also associated with increased motor activity during the day which might lead to an increased total energy expenditure.

After adenotonsillectomy these alterations are normalized. The meta-analysis for differences in before and after weight, which was based on 11 studies enrolling a total of 390 children, showed that the operation favored weight increases in addition to resulting in an increased height velocity and increases in IGF-1 and IGFBP-3 serum concentrations.

This review focused on longitudinal growth and growth biomarker changes after adenotonsillectomy. However, it also evaluated the changes in weight.

These results of clinical studies open an interesting field of research involving sleep disordered breathing and the regulation of longitudinal growth, appetite, and energy homeostasis.

Clinical review: treatment of pediatric obesity: a systematic review and meta-analysis of randomized trials

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Background: The Endocrine Society decided to formulate clinical practice guidelines for the management of pediatric obesity. In doing so, it formed a task force to develop these recommendations.

Methods: In a first step a systematic review of the literature on the treatment of pediatric obesity was conducted. Literature was searched until February 2006. Eligible studies were randomized trials of overweight children and adolescents assessing the effect of nonsurgical interventions on obesity outcomes.

Results: Short-term medications were effective as demonstrated for sibutramine and orlistat. In addition studies focusing on an increase in physical activity also showed moderate effects on the reduction of percent body fat only. Combined lifestyle interventions led to small changes in BMI.

Conclusions: This report briefly summarizes the findings of a systematic review and a meta-analysis of randomized trials. It can be concluded that medications and combined lifestyle interventions show short-term efficacy with small changes in overweight. The long-term efficacy and safety of such treatment programs is unclear.

Clinical review: behavioral interventions to prevent childhood obesity: a systematic review and metaanalyses of randomized trials

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Background: Experts have implicated both physical activity and dietary behavior in the causal path of obesity. Consequently targeting these lifestyle behaviors have been the aims of studies to prevent childhood obesity. However, the efficacy of such programs to prevent pediatric obesity remain unclear so far.

Methods: A literature search was performed until February 2006. Eligible studies were randomized trials assessing the impact of interventions on both lifestyle behaviors and body mass index (BMI).

Results: The available randomized controlled trials to prevent pediatric obesity showed that small changes in their respective target behavior can be achieved. However, this is not associated with significant changes in BMI compared with controls. Further exploration through hypothesis-generating subgroup analysis found: (1) there was no sex-treatment interaction; (2) trials in children found larger reductions in sedentary activity than trials in adolescents; (3) trials of treatments for >6 months found larger reductions in sedentary activity and BMI than shorter trials, and (4) no significant interaction was found between interventional components and their effect on target behaviors or BMI compared with controls.

Conclusion: Obesity prevention programs may cause small changes in target behaviors but no significant effect on BMI compared with controls.

Prevention and treatment of pediatric obesity: an endocrine society clinical practice guideline based on expert opinion

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Background: The Clinical Guideline Subcommittee of the Endocrine Society identified pediatric obesity as a priority area requiring practice guidelines and appointed a task force to formulate evidence-based recommendations.

Methods: The task force uses systematic reviews of available evidence to give key recommendations. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method was applied.

Results: Each recommendation given is followed by a description of the evidence, the values that panelists considered in making the recommendation, and in some instances remarks with technical comments or caveats.

Conclusion: These recommendations are very helpful for practitioners treating obese children and for people of the public health system involved in prevention programs for pediatric obesity.

Interventions for treating obesity in children (review)

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Background: More information is needed about the best way to treat obesity in children and adolescents.

Methods: A literature research was performed (1985 to May 2008). Defined selection criteria were applied.

Results: 64 studies were included (54 studies on lifestyle treatments and 10 studies on drug treatments). No surgical treatment studies were suitable to include in this review. The analysis of study data showed that lifestyle programs can slightly reduce the level of overweight 6 and 12 months after the beginning of the program. There is an additional effect of orlistat and sibutramine, although a range of adverse effects was also noted. There are not sufficient data on the long-term outcome of such treatment programs.

Conclusion: Combined behavioral lifestyle intervention compared to standard care or self help can produce significant and clinical meaningful reduction in overweight in children and adolescents during the first months.

Huge efforts have been made to review and analyze the available results from studies investigating the effect of treatment programs and prevention programs on childhood overweight and obesity. It is a valuable result of all the above-mentioned reviews that these data have been put together and the main outcomes are now easily available for practitioners and scientists in the field.

However, it has to be concluded that so far all efforts comprising intensive multi-professional long-term (up to 12 months) care result only in modest reductions in overweight. In addition the effective programs are only available for a minority of the children and the large majority of obese children and adolescents is not able to enter in such programs due to lack of motivation and social, familial, or financial support.

Therefore new ways have to be found to tackle the problem of childhood obesity probably with an emphasis on public health measures aiming at changing the living environment of these children.

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