Obesity and Weight Regulation

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Covering the abundance of obesity literature is not an easy task. The increasing number of papers published in this field is a challenge since evidence of obesity spreads across many journals as shown in an interesting study by Baier et al. [1]. These authors showed that obesity journals capture only a small proportion of the literature on clinical obesity care. Reading the *International Journal of Obesity*, *Obesity Surgery*, and *Obesity (Silver Spring, Md)* will capture less than 20% of the research articles related to overweight and clinical obesity.

The highlights in the this year's chapter are papers about new developments in the field of extreme obesity in adolescents, a review in *Science* and several articles about circadian integration of metabolism and energetics, and last but not least, a large number of articles on brown adipose tissue (BAT). The research in the field of BAT has been initiated by three articles in the *NEJM* [2–4] and has been discussed in the *Yearbook 2009* [5] and has been followed up in the *Yearbook 2010* [6]. The renaissance of BAT is followed by a wave of research projects leading to unpredictable results [7].

Development of obesity prevalence rates: extreme obesity is the major issue

Obesity prevalence – up, down, or sideways?

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N Engl J Med 2011;364:987–9.

Perspective: The authors refer to two publications published in 2010 in *JAMA* by Flegal et al. [8] and Ogden et al. [9] which describe a stabilization of the prevalence of obesity with no further increase as shown over the past 10 years for adults and for children. In contrast to these two reports, others still demonstrate an increase in prevalence numbers over the recent years. The discrepancies among the estimates may be explained by a simple difference in data collection methods. The data published in *JAMA* are data from the NHANES studies which measured heights and weights each year. Other reports are based on self-reported heights and weights. The fact that these data seem to show a further increase in prevalence might be explained by the fact that fewer people are reporting lower-than-accurate weights thanks to the increased awareness about obesity on the part of healthcare professionals and the public at large [10].

The stabilization of obesity prevalence is interesting, however this stabilization occurs on an unacceptable high level. Reasons for the stabilization might be the fact that there is a general increasing recognition of this health issue by healthcare professionals, schools, community organizations, industry, and governments. Possibly this leads to a reduction in environmental factors which contribute to inappropriate weight gain. Another explanation could be that after several years of life, conditions which support inappropriate weight gain in all people who have a strong genetic susceptibility to weight gain are already obese, while a resistant group remains lean [8, 9].

When regarding the latter possible explanation it is important to recognize that although a stabilization of prevalence rates is obvious, an increase in the prevalence of extremely obese adults, children, and adolescents is still occurring. This leads to an increasingly skewed distribution of BMI values to the right.

A stabilization and even a reduction in the prevalence rates of overweight and obesity in children and adolescents has also been reported in several other countries in the Western world [9, 11–14]. Scientifically, it is worthwhile to further investigate this trend and to analyze possible causal factors.

Prevalence of extreme obesity in a multiethnic cohort of children and adolescents

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J Pediatr 2010;157:26–31.

Background: There exists only few scientific data about extreme obesity in childhood and adolescents at the population level. It has been shown that although the prevalence rates of obesity seems to have stabilized in several countries in the last years, the number of extremely obese children and adolescents is still increasing.

Methods: Data on measured weight and height were taken from electronic medical records of more than 700,000 patients (age 2–19 years) (88% of eligible patients) who have been part of an integrated pre-paid health plan in 2007 and 2008 in Southern California. Extreme obesity has been defined as BMI-for-age ≥ 1.2 times 95th percentile or BMI ≥ 35 kg/m².

Results: 7.3% of the boys and 5.5% of the girls were extremely obese. Prevalence of extreme obesity was dependent on the ethnic group and on age. The highest prevalence rates were seen in Hispanic boys and in African-American girls.

Conclusions: Extreme obesity is a frequent finding in children and adolescents. The numbers show a shift towards extreme obesity. Due to the high persistence of extreme obesity into adulthood, these numbers reflect an enormous burden of adverse health outcomes.

This population-based cross-sectional study gives valuable information on the prevalence of extreme obesity in children and adolescents in Southern California, where current-day lifestyle prevails and American-Hispanics are a majority. 7.3% of the boys and 5.5% of the girls were extremely obese. Prevalence of extreme obesity was dependent on the ethnic group and age. The highest prevalence rates were seen in Hispanic boys and in African-American girls.

Due to the high numbers, extreme childhood obesity becomes a serious issue in pediatric care. The concept of 'pack-years' for smoking patients can be taken over for extremely obese children who may experience cumulative effects of their 'pound-years' [15, 16]. After having such numbers in hand it would be important to investigate in further studies the economic burden and the health consequences of extreme obesity in childhood and adolescence. There are only two studies published so far which have addressed the additional health consequences of extreme obesity compared with moderate obesity in children [17, 18]. These studies clearly show that the prevalence of the metabolic syndrome is higher in the extremely obese group (prevalence of the metabolic syndrome 30% in moderately obese and 50% in extremely obese) [18].

Association of adolescent obesity with risk of severe obesity in adulthood

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JAMA 2010;304:2042–47.

Background: Severe or extreme obesity is associated with a higher risk of life-threatening complications, including diabetes, hypertension, dyslipidemia, asthma, and arthritis. The prevalence of extreme obesity is still increasing in adults and children. This study investigated the association of adolescent obesity and the risk of severe obesity in adulthood defined by BMI >40 kg/m².

Methods: A cohort of more than 8,800 individuals (age 12–21 years), participants of the US National Longitudinal Study of Adolescent Health, were followed up as adults (ages 18–24 and 24–33 years).

Results: 60 of 79 severely obese adolescents in 1996 remained severely obese in adulthood. By 2009, 703 moderately obese adolescents had become severely obese in adulthood.

Conclusion: This study from a nationally representative sample shows a high incidence of severe obesity during the transition from adolescence to adulthood. Given the comorbidities and chronic diseases associated with severe obesity, the clinical implications of these data are concerning.

These data show a strong persistence of severe obesity from adolescence into young adulthood. Furthermore, the incidence of severe obesity during the transition from adolescence to adulthood is high. These results demonstrate the need for prevention of severe obesity early in life. Interventions prior to adolescence should aim at limiting the progression of inadequate weight gain. Although this need is clearly recognized, there are currently no convincing intervention strategies to reach this aim at the public health level in most countries. Changes of diet and exercise on the basis of behavioral modifications do not result in sufficient effects on body weight. Even when they are combined with pharmacotherapy only a 5–10% reduction in weight in adults can be achieved without convincing long-term data. There are no studies showing that such results can be obtained in obese adolescents except for some short-term studies. Currently, only bariatric surgery is a treatment method leading to dramatic weight losses and to a positive long-term success in relation to quality of life and adverse effects of obesity. Data on the risks and benefits of bariatric surgery in adolescents are insufficient to support a recommendation for this treatment option in general. However, some individuals with severe obesity in adolescence may profit from such a procedure in the long term.

Trends and outcomes of adolescent bariatric surgery in California, 2005–2007

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Background: Adolescents with extreme obesity are a serious health challenge. Bariatric surgery has been shown to be the only effective treatment in extremely obese adults leading to meaningful weight reduction. Due to this fact, bariatric surgery is more and more frequently applied to extremely obese adolescents. This study focused on trends and outcomes of adolescent bariatric surgery in California, 2005–2007.

Methods: By means of the statewide Health Planning and Development database, patients <21 years of age who underwent elective bariatric surgery have been identified.

Results: Between 2005 and 2007, 590 adolescents (aged 13–20 years) underwent bariatric surgery in 86 hospitals. During this short period of time, the rates of laparoscopic adjustable gastric banding (LAGB) increased 6.9-fold from 0.3 to 1.5 per 100,000 population. In the same time, laparoscopic Roux-en-Y gastric bypass (LRYGB) rates decreased from 3.8 to 2.7 per 100,000 population. The rate of major complications in the hospitals was 1%, and no deaths were documented. 4.7% of the patients with LAGB had band revision, 2.9% of the LRYGB had reoperations. Interestingly, white adolescents accounted for 65% of the operations while representing only 28% of those were overweight. Self-payers preferred LAGB more than privately insured adolescents. The majority (78%) of the adolescents using bariatric surgery were female.

Conclusions: In the USA, LRYGB is the standard of care for morbidly obese adolescents who seek surgical intervention and LAGB is not yet approved by the Food and Drug Administration (FDA) for use in adolescents younger than 18 years. Nevertheless, the LAGB procedure has dramatically increased in the last years even overtaking LRYGB and becoming the most frequently performed bariatric procedure in this age group.

Earlier results with laparoscopic adjustable gastric banding (LAGB) have indicated that this bariatric surgery procedure is safe and effective [19–22]. The only randomized controlled trial, published in *JAMA* [19] and reported in the *Yearbook 2010* [6], proved that LAGB is an effective intervention for severely obese adolescents leading to substantial and durable reduction of obesity and to better health. The dramatic shift shown in this study towards an increased application of LAGB and a decrease in the number of adolescents receiving laparoscopic Roux-en-Y gastric bypass (LRYGB)

shows that although not approved by the FDA, this procedure gains confidence. The low numbers of complications and the lack of any reported deaths support the decision for the application of LAGB. However, as for LRYGB, long-term results need to be evaluated. Whereas LRYGB may have severe long-term complications due to malnutrition, LAGB may lead to severe long-term problems by enlargement of the stomach above the band or injury to the tubing. Eating small meals slowly is central to avoiding this problem after the gastric banding procedure. Whether these changes in eating behavior are feasible over long-term periods remains an open question. For adolescents, additional education and supervision of eating are necessary to reduce the need for revisions.

Childhood obesity

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Lancet 2010;375:1737–48.

Review – Seminar

A seminar is generally a form of academic instruction which typically is organized in a recurrent way. Eight years ago the last seminar on childhood obesity was published in *The Lancet* [13]. The aim of this review was to provide a seminar summarizing the most recent findings within a seminar on childhood obesity and outlining some of the remaining challenges.

The seminar provides recent data on the epidemiology of childhood obesity on determinants and risk factors, on differential diagnoses and complications, on the issue of prevention and non-pharmacological treatment, and finally on possible pharmacological and surgical treatment options. There is a large table in the review on determinants or risk factors for the development of childhood obesity or increased adiposity which is of high value since it summarizes all known determinants and comments on each of the determinants or risk factors with respect to the potency for modification and the type of evidence.

Rock around the clock

Review: circadian integration of metabolism and energetics

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Science 2010;330:1349–54.

Organisms show a large number of physiological and behavioral rhythms that recur every 24 h. Circadian clocks align the related behavioral and biochemical processes with the day/night cycle. In the last few years it has become possible to genetically interfere with these processes leading to a transformation of biological timing through genetic disruption of so-called clock genes. It has been shown that the disruption of the circadian rhythm, which is a characteristic of the modern world, leads to metabolic pathologies. The scientific knowledge on the relationship between circadian rhythms, sleep deprivation, obesity, and diabetes has increased in the last couple of years. The new knowledge presents implications for rational treatment of these conditions.

This review summarizes the current knowledge on circadian integration of metabolism and energetics with special focus in the molecular coupling between metabolic and clock networks and its relevance to gene environment and brain behavioral systems important in energy balance and metabolic disease.

The review summarizes findings on core transcriptional components of the clock and posttranslational regulation. It describes major players in the crosstalk between the clock and metabolic tran-

scription networks: Nuclear hormone receptors and the phase alignment of metabolic gene expression cycles, direct versus indirect role of clock transition factors in metabolic gene regulation, reciprocal control of clock by metabolic signaling. The review shows how circadian disruption causes metabolic pathologies by summarizing results from experiments with genetic models and results of human clinical studies. Interestingly, in humans it could be shown in a clinical study that when individuals are exposed to a light/dark cycle lengthened to 28 h the sleep/wake cycle is also driven at 28 h. However, the melatonin and body-temperature rhythm still runs with a 24-hour period [23]. Such data show that forces leading to desynchronization as happens in periods with jetlag or shift work can lead to impaired glucose tolerance and hypoleptinemia. Further studies are needed to show that the circadian disruption in an experimental setting affects endocrine pancreas insulin secretion, hepatic gluconeogenesis, and glucose disposal in skeletal muscles.

The major findings of the last years with respect to chronobiology and pathophysiology in metabolism and energetics include: (1) the connection between brain and peripheral tissue clocks in metabolic homeostasis, (2) the interplay between circadian and sleep disruption in energetics, (3) the relationship between nutrient state and circadian homeostasis, and (4) the impact of circadian clock systems on human physiology.

Further details on recent findings, specifically on chronobiology and endocrine systems for the pathophysiology of obesity, have been published recently elsewhere [24, 25].

Light at night increases body mass by shifting the time of food intake

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Proc Natl Acad Sci USA 2010;107:18664–9.

Background: Increase of light exposure at night (LAN) and shift work coincide with the global increase in the prevalence of obesity and metabolic disorders. Light information synchronizes an endogenous biological clock which controls circadian regulation of energy homeostasis. Any disruption of clock function causes circadian and metabolic disturbances.

Methods: The authors investigated the effect of LAN in two different settings. In the first experiment, male mice were divided into three groups: group 1 (LL) was exposed to 24 h of constant light (150 lx); group 2 (LD) had a standard light dark cycle (16 h of light (150 lx), 8 h of dark), and group 3 (DM) was exposed to 16 h of light and 8 h of dim light (5 lx). Food intake and activity was assessed daily and body mass was calculated each week. The second experiment differed in terms of food availability. Instead of ad libitum, food was restricted to either normal activity time or normal rest time.

Results: Mice of all three groups had comparable levels of caloric intake and total daily activity output. Importantly, mice housed in either bright (LL) or dim (DM) LAN had significantly increased body mass and reduced glucose tolerance compared with mice in a standard (LD) light/dark cycle. Additionally, DM and LL mice showed a different timing of food consumption compared to LD mice. Nocturnal rodents typically eat considerably more food at night, however DM mice consume 55.5% of their food during the light phase, as compared to 36.5% in LD mice. Body mass gain in DM mice was prevented when food consumption was restricted to the active phase.

Conclusion: These data suggest that low levels of LAN disrupt the timing of food intake, leading to excess weight gain. The authors conclude that exposure to LAN and the resulting changes in the daily pattern of food intake and activity are contributing factors to the coincidence between prolonged computer use and television viewing and obesity in humans.

In the present study the authors found that mice gained 50% more body mass over 8 weeks when they were exposed to dim light in the night compared to mice with a standard dark-light-cycle. This enhanced body mass gain could not be explained by lower activity levels or higher food intake. In fact, mice just ate at times they normally would not. When food was restricted to normal eating times, excess weight gain was prevented in mice housed with dim light at night. The authors suggest here another possible explanation for the increasing prevalence of obesity in Western countries. We are exposed to dim light at night by prolonged computer use and television viewing which have already been identified by researchers to be obesity risk factors. Nevertheless, research has focused

on the lack of activity that goes along with these habits. The authors hypothesize that people who sit in front of the television or computer at night eat at the wrong times, thereby disrupting their whole metabolism. Obese children certainly do so. This might lead to weight gain despite maintaining a good energy balance. The comparison of nocturnal animals with humans, however, may be premature. Confirmation of these results in humans is mandatory.

New mechanisms

Rescue of obesity-induced infertility in female mice due to a pituitary-specific knockout of the insulin receptor

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Cell Metab 2010;12:295–305.

Background: Obesity and insulin resistance are not only associated with diverse metabolic complications but also with a high rate of infertility in women. The pathophysiological mechanism for this infertility is however only partially explored.

Methods: The authors generated a mouse model with specific knockout of the pituitary insulin receptor (PitIRKO) and compared these mice to wild-type (WT) mice, while both were either chow fed or on a high-fat diet leading to diet-induced obesity (DIO).

Results: WT and PitIRKO mice on high-fat diet developed similar levels of elevated fasting blood glucose, insulin and leptin. Female WT-DIO mice were infertile with irregular estrous cyclicity and elevated LH levels (basal and stimulated), as known from previous experiments. Female lean PitIRKO mice cycled regular, showed the same reproductive rate as lean WT mice, and had comparable basal and stimulated LH levels. Female PitIRKO-DIO mice also cycled regular and had normal basal LH levels. However, they showed a reduced stimulated LH and their reproductive rate lay between that of lean mice (WT and PitIRKO) and WT-DIO mice. LH levels of lean WT and WT-DIO mice rose after infusion of insulin. In contrast, PitIRKO-DIO mice showed no rise in LH after insulin infusion.

In muscle and liver cells, DIO mice (PitIRKO and WT) showed low p-AKT levels before and after treatment with insulin, compatible with insulin resistance. However in the pituitary gland, p-AKT levels were elevated in WT-DIO mice and rose further after insulin infusion, whereas PitIRKO-DIO mice had considerably lower pituitary p-AKT levels which could not be stimulated.

Conclusion: The increase in pituitary p-AKT and LH levels in WT-DIO mice after insulin infusion indicates that the pituitary remains insulin-sensitive even in the face of general insulin resistance. Mice with specific knockout of pituitary insulin receptors develop a normal peripheral insulin resistance under a high-fat diet, but their fertility is at least partially preserved. This suggests a role for increased pituitary insulin signaling in the development of obesity-induced infertility.

With the limitation in mind that results from experiments with mice cannot be directly transferred onto mankind, the authors here still provide a valuable piece of information on the consequences of obesity.

The fact that insulin/IGF-1 signaling is necessary for normal reproductive function has already been shown by Burks et al. [26], who proved that deletion of insulin receptor substrate-2 (IRS-2) causes female infertility. The same group developed mice with neuron-specific disruption of the insulin receptor gene and found impaired spermatogenesis and ovarian follicle maturation. A normal LH release after exogenous gonadotropin treatment indicated a hypothalamic defect in these mice [27].

In this study, the differential action of insulin in the brain is analyzed in further detail by the generation of mice with specific pituitary insulin receptor knockout (PitIRKO), which reduced obesity-induced infertility. However, the fertility rate of PitIRKO on diet-induced obesity (DIO) mice was not completely normal in contrast to lean PitIRKO mice. This indicates that the obesity of the PitIRKO-DIO mice must have further negative effects on the reproductive system, either on the hypothalamus or

on the ovarian tissue. In fact, insulin has been shown to augment not only basal production of estradiol and progesterone, but also LH-stimulated steroid accumulation in granulosa cell cultures even in women suffering from PCO. This implies that increased insulin signaling in the pituitary gland and maybe also in the ovaries explains at least some aspects of obesity-induced infertility.

Unfortunately, for obese women struggling to become pregnant, these exciting new findings so far provide no further help. It seems unlikely that specific pituitary or ovarian insulin antagonists can be developed. Our new knowledge on the deleterious effects of hyperinsulinemia on fertility therefore leads to the old conclusion that the best cure is a healthy lifestyle with a reduction of body weight and insulin levels.

Glucose and weight control in mice with a designed ghrelin O-acetyltransferase inhibitor

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Science 2010;330:1689–92.

Background: The gastric hormone ghrelin stimulates weight gain in mice and humans. Ghrelin is activated by octanoylation on Ser³. This posttranslational modification is catalyzed by the enzyme ghrelin O-acetyltransferase (GOAT).

Methods: An antagonistic peptide-based bisubstrate analogue GO-CoA-Tat was designed, synthesized and characterized.

Results: GO-CoA-Tat inhibited GOAT function in vitro and in HeLa and HEK cells. WT C57BL6 mice intraperitoneally treated with this GO-CoA-Tat displayed lower acyl ghrelin levels along with lower body weight and lower fat mass, but same food intake. This treatment had no effect on ghrelin knock-out C57BL6 mice. In addition, C57BL6 mice treated with a lower dose of GO-CoA-Tat displayed a significant increase in insulin secretion and decrease in blood glucose level. In addition, blocking GOAT downregulated UCP2 mRNA in the mouse islets, but not in the stomach.

Conclusion: This study supports the relevance of acyl ghrelin in the regulation of obesity and type 2 diabetes. Pharmacological inhibition of GOAT might provide a useful strategy to cure metabolic disorders.

Acyl ghrelin, which ameliorates appetite, has been an intensively studied target molecule for the treatment of obesity. However strategies to target the active, acylated form of ghrelin failed. The discovery of the enzyme ghrelin O-acyltransferase (GOAT) facilitated the development of specific acylation inhibitors of ghrelin and thereby preventing activation of its receptor, the growth hormone secretagogue type 1a (GHSR1a). The authors of this study designed the first GOAT antagonist which efficiently inhibited formation of acyl ghrelin in vitro and in vivo.

Direct targeting of acyl ghrelin biosynthesis offers several advantages: acylation is blocked at the periphery and does not need to cross the blood-brain barrier. Specific inhibition of acyl ghrelin synthesis does not affect des-acyl ghrelin function, whereas blocking of receptors may affect acyl ghrelin formation and other signaling pathways.

Improving the pharmacodynamic and pharmacokinetic properties of peptide-based agents, such as GO-CoA-Tat, a peptide-based bisubstrate analog that antagonizes GOAT, have the potential to become agents for weight regulation.

Brown adipose tissue activity controls triglyceride clearance

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Nat Med 2011;17:200–5.

Background: Brown adipose tissue (BAT) uses fatty acids for heat production in order to defend the body against cold and has recently been shown to be present and active in humans. Triglyceride-rich lipoproteins (TRLs) are vehicles for lipid transport in the bloodstream where fatty acids are released by lipoprotein lipase (LPL). While fatty acids are taken up by peripheral organs such as muscle and adipose tissue, remnant particles which are rich of cholesterol are cleared by the liver. These remnant particles together with elevated plasma triglyceride concentrations are risk factors for cardiovascular disease. It remains unclear so far how the uptake of TRLs is mediated by BAT mechanistically.

Methods: TRL organ distribution was measured in vivo by using TRLs labeled with radioactive triolein and superparamagnetic iron oxide nanocrystals. Additionally, TRL uptake was monitored real-time by intravital confocal microscopy.

Results: The authors could show that activation of BAT in mice by cold exposure accelerated plasma clearance of triglycerides. This was based on an increased uptake of triglycerides into BAT and was dependent on LPL activity and CD36 expression. In models of diet-induced obesity and insulin resistance, cold exposure led to a reduction of both hyperlipidemia and insulin resistance.

Conclusion: The activity of BAT controls vascular lipoprotein homeostasis by inducing TRL turnover and channeling lipids into BAT. Activation of BAT might be a therapeutic option to reduce plasma triglycerides and prevent human obesity.

Brown adipose tissue is present and active in humans, and its important role in plasma glucose uptake has been shown in humans by fluorodeoxyglucose positron emission tomography [4]. The precise mechanism of lipoprotein clearance by BAT has been, however, not elucidated so far. By using the elegant technique of intravital confocal imaging, Bartelt et al. demonstrated the rapid uptake of triglyceride-rich lipoproteins, which was further enhanced by cold exposure of the animals. This effect was shown to rely on enhanced endothelial permeability. Furthermore, it was dependent on LPL and CD36 activity. In a mouse model of lipodystrophy, cold exposure corrected plasma lipid concentration within hours. Given the low percentage that BAT contributes to body mass (5%), its role in triglyceride clearance is enormous and it obviously plays a major role in regulating body fat mass. This study clearly points out the potential role of BAT in preventing risk factors of the metabolic syndrome – obesity and their related disorders.

If this model can be transferred to the human system in further studies, it will enhance the ambition to increase BAT amount and activity in humans for use as a therapy against obesity.

Knockdown of NPY expression in the dorsomedial hypothalamus promotes development of brown adipocytes and prevents diet-induced obesity

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Background: Neuropeptide Y (NPY) is secreted by the hypothalamus and regulates several physiologic processes including regulation of energy balance. In contrast, the role of NPY in the dorsomedial hypothalamus (DHM) remains unclear.

Methods: NPY was knocked down by direct delivery of adenoviral shRNA constructs against the NPY gene into the DHM of rats.

Results: Knockdown of DHM NPY led to a reduction of fat depots and to the development of brown adipocytes in the inguinal adipose tissue depot of the animals. Moreover, the expression of uncoupling protein (UCP)-1 increased in both inguinal and brown adipose tissue. This led to an induction of energy expenditure and enhanced non-shivering thermogenesis in response to cold. It also increased activity, improved insulin sensitivity and glucose homeostasis.

Conclusion: NPY in the DHM is involved in body weight regulation by mediating brown adipocyte development via the sympathetic nervous system.

It has already been shown that the DHM is involved in body temperature control and non-shivering thermogenesis [28]. However, the neural mechanisms underlying these actions are still undetermined. Here, the authors demonstrate that knockdown of DHM NPY leads to an increase in brown adipocytes in the inguinal white depot of rats accompanied by an increase of norepinephrine concentration in this tissue. Moreover, sympathetic denervation with the neurotoxin 6-hydroxydopamine resulted in a marked decrease of brown adipocyte formation. If this could be transferred to the human system, the DHM would be an interesting target for therapy aiming at combating obesity and/or the metabolic syndrome.

Identification of inducible brown adipocyte progenitors residing in skeletal muscle and brown fat

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Proc Natl Acad Sci USA 2011;108:143–8.

Background: Brown adipose tissue (BAT) is able to increase energy expenditure upon cold induction and has therefore been proposed to function as a defense against obesity. Advances have been made during the last years in revealing the transcriptional regulation of brown adipocyte differentiation, however the developmental signals responsible for brown fat cell fate and the specification of cellular lineage remain poorly understood.

Methods: The authors identified and isolated adipogenic progenitor cells (Sca-1+ progenitor cells, ScaPCs) from murine brown and white adipose tissue and skeletal muscle by selecting for specific surface markers.

Results: ScaPCs from interscapular BAT were constitutively committed brown-fat progenitors, but even ScaPCs from skeletal muscle and subcutaneous white fat were highly inducible to differentiate into brown-like adipocytes upon stimulation with bone morphogenetic protein 7 (BMP7). Moreover, isolated human preadipocytes from subcutaneous white adipose tissue showed the highest capacity to undergo brown adipogenic differentiation compared to cells from mesenteric or omental white fat. BMP7-treated ScaPCs from skeletal muscle developed brown fat-specific characteristics when re-engrafted into skeletal muscle of syngeneic mice. Interestingly, ScaPCs isolated from obesity-resistant mice displayed higher thermogenic capacity compared to cells from obesity-prone animals.

Conclusion: This study characterizes the molecular attributes of adipose progenitors from different tissues and demonstrates the dynamic interplay between these progenitors and inductive signals in the recruitment of BAT.

Lineage studies have shown that brown adipocytes – like myoblasts – derive from progenitors expressing the myogenic marker *myf5*, whereas white adipocytes derive from *myf5*-negative cells of the lateral mesoderm [29, 30]. Furthermore, brown adipocytes reside in white adipose tissue and skeletal muscle. It is shown in this study that adipogenic progenitor cells from different tissues are able to induce a brown fat cell program upon treatment with bone morphogenetic protein 7 (BMP7), a factor crucial for brown fat cell development. The extent of induction was thereby dependent on the tissue source. After transplantation into skeletal muscle, BMP7-treated progenitors generate fat pads with brown fat characteristics. However, brown fat formation was dependent on the microenvironment, since transplantation into subcutaneous adipose tissue led only to a minor extent of BAT formation. This study suggests a cell-based approach to generate energy-consuming cells for anti-obesity treatment. The next step would be here to isolate human adipocyte precursors from skeletal muscle and treat these cells with BMP7 in order to re-transplant them for recruitment of brown adipose tissue. The

ability of brown adipose tissue to increase energy expenditure holds the option to treat obesity and its related comorbidities by enhancing differentiation of brown adipocytes from progenitor cells.

Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice

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Background: White adipose tissue can be classified into subcutaneous and several intra-abdominal depots. Expansion of these abdominal depots is associated with high risk for metabolic disease in both rodents and humans, while excess subcutaneous white adipose tissue mass does not carry the same risks. Brown adipose tissue produces heat by non-shivering thermogenesis and it has been shown that the appearance of brown-like adipocytes in white adipose tissue is associated with an improved metabolic phenotype. Therefore, understanding of the function of these different cell types may be critical to establish new therapeutic perspectives for metabolic disease.

Methods: Transgenic mice overexpressing the brown adipose determination factor Prdm16 in the adipose tissue or Prdm16-deficient mice were used for this study.

Results: The authors could show that Prdm16 is selectively expressed in subcutaneous adipose tissue compared to abdominal white adipose tissues in mice. Transgenic mice overexpressing Prdm16 in adipose tissues displayed the development of brown adipocytes exclusively in the subcutaneous tissue. Additionally, these animals had an improved metabolic phenotype including increased energy expenditure, limited weight gain and improved glucose tolerance under a high-fat diet. Depletion of Prdm16 in isolated subcutaneous adipocytes led to a decreased expression of brown adipocyte marker genes and to a reduction of uncoupled cellular respiration. Moreover, mice which were haploinsufficient for Prdm16 displayed a phenotype with less brown adipocytes in white adipose tissue.

Conclusion: The authors conclude that Prdm16 is a factor which determines a brown-like fat gene program and thermogenesis in subcutaneous adipose tissues.

These authors were the first who identified the role of Prdm16 in brown adipose development and already published several high-ranking articles on this topic [31–33]. This gene has been described to be a molecular switch between skeletal muscle and brown adipose tissue differentiation and is highly expressed in brown adipose tissue. In this article, the impact of Prdm16 on white adipose tissue has been studied. Interestingly, Prdm16 is selectively expressed in the inguinal adipose depot, whereas in humans it is expressed only in uterus and fetal kidney. Transgenic expression dependent on an adipose promoter in mice resulted in increased appearance only in this depot and led to an improved metabolic phenotype. Prdm16-deficient cells partially lose their brown fat phenotype despite adrenergic stimulation.

The precursor cells for brown fat-like adipocytes in white adipose tissue are not known so far. This study would support a scenario in which mature adipocytes could be driven to express genes characteristic to brown adipocytes. However, it does not exclude the existence of alternative progenitor cells for brown adipocytes in white adipose tissue such as preadipocytes or fibroblasts.

Acute stimulation of white adipocyte respiration by PKA-induced lipolysis

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Diabetes 2010;59:2474–83.

Background: Brown adipose tissue is the site of non-shivering thermogenesis in mammals by uncoupling of mitochondrial respiration. It has been shown that white adipose tissue (WAT) is also capable of mitochondrial uncoupling upon catecholamine stimulation. The role of lipolysis and of fatty acids in this context and the molecular mechanisms of WAT uncoupling remain unclear, especially in human adipocytes.

Methods: The effects of β -adrenergic receptor activation and cAMP-elevating agents on respiration and mitochondrial uncoupling was examined by measuring oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) in human adipocytes. Additionally, mitochondrial depolarization, lipolysis and kinase activities were determined in gene knockdown or targeting approaches.

Results: Oxidative and glycolytic respiration was increased together with mitochondrial depolarization in human and mouse white adipocytes upon stimulation with isoproterenol (ISO), forskolin (FSK) or dibutyryl-cAMP (DB). OCR increase was dependent on protein kinase A (PKA)-induced lipolysis and insensitive to ATPase inhibition by oligomycin. Increased OCR and uncoupling was blunted by inhibition of the mitochondrial permeability pore (PTP) and its regulator, Bax. Interestingly, OCR and uncoupling in response to ISO in white adipocytes from obese subjects were reduced in comparison to control adipocytes from lean subjects.

Conclusion: Mitochondrial uncoupling occurs in white adipocytes by gating PTP under regulation by Bax.

BAT contributes to body thermo- and energy regulation by uncoupling the mitochondrial respiratory chain. This mechanism is dependent on the release of free fatty acids (FA) by lipolysis. Also other tissues such as muscle and liver are capable of mitochondrial uncoupling and have been extensively studied in terms of FA uncoupling. The role of FA in white adipose tissue uncoupling, especially in human adipocytes, is unclear.

In this study, the authors show that mitochondrial uncoupling is functional in white adipocytes and is dependent on permeability pore and its regulator Bax, providing a possible mechanism of uncoupling in white adipocytes. Additionally, uncoupling in obese subjects seems to be disturbed. Even a slight increase in mitochondrial uncoupling in this tissue might contribute to sustained enhancement of energy expenditure. This would be also in line with the recent discovery of active BAT in adult humans.

News from white adipose tissue

Regional impact of adipose tissue morphology on the metabolic profile in morbid obesity

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Diabetologia 2010;53:2496–503.

Background: Not only the total amount, but also the regional distribution of adipose tissue plays an important role in the pathogenesis of obesity-related disorders such as insulin resistance and dyslipidemia. There is accumulating evidence that adipose tissue morphology, i.e. the size and number of fat cells, is an additional important key player in the development of these complications.

Methods: A group of 80 morbidly obese females undergoing gastric bypass surgery were studied. Total body fat and fat distribution was studied by DEXA. Lipid and glucose metabolism markers were studied in venous blood samples. The diameter of adipocytes isolated from visceral and subcutaneous adipose tissue samples was determined.

Results: Visceral, but not subcutaneous, fat cell size was associated with lipid markers (plasma apolipoprotein A, total cholesterol, LDL cholesterol, triacylglycerols). Subcutaneous, but not visceral, fat cell size was associated with plasma insulin/glucose and insulin sensitivity. The associations were independent of age, BMI, fat mass and fat distribution. Adipose tissue hyperplasia (i.e. many, but small fat cells) was associated with better insulin sensitivity and better lipid profiles compared to adipose hypertrophy (i.e. few, but large fat cells). Systemic markers of inflammation were related to fat cell size.

Conclusions: Not only adipose tissue mass and distribution, but in a depot-specific manner also the size of fat cells is related to metabolic comorbidities in human morbid obesity. Large fat cells in visceral adipose tissue are more linked to a dyslipidemic profile. Large fat cells in the subcutaneous depots are more related to insulin resistance.

Peter Arner from the Karolinska Institute in Stockholm has longstanding expertise in studying adipose tissue metabolism. He is one of the trendsetters in the field of obesity research. Already more than 30 years ago he studied the relationship between fat cell size and fat cell metabolism. He was also one of the first scientists to propose regional differences in fat cell function.

Recently, his work has gained enormous attention. By measuring the incorporation of radioactivity from the atmosphere into cellular DNA, he and his co-workers determined the age of fat cells [34]. The scientists found that around 10% of all fat cells are replaced every year. The formation of new fat cells is counterbalanced by the elimination of already existing fat cells by apoptosis. The total number of adipocytes in the body however seems relatively stable independently of age, sex, and body mass index. According to Peter Arner's findings, changes in adipose tissue mass, for example after marked weight reduction, are mainly attributable to changes in adipocyte volume. This finding led to a renaissance of studying the effects of fat cell volume on adipose tissue function and whole-body metabolism.

Interestingly, the volume of fat cells impacts on metabolism in a depot-specific manner. While large fat cells in the visceral depot increase the risk for dyslipidemia, large cells in the subcutaneous depot decrease insulin sensitivity. Intensive research is needed to understand the underlying mechanisms of these depot-specific effects. In general, having many, but smaller adipocytes protects from metabolic complications. Thus, it is of great interest to identify molecular targets which might induce switching from a hypertrophic toward a hyperplastic phenotype.

Fibrosis in human adipose tissue: composition, distribution, and link with lipid metabolism and fat mass loss

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Diabetes 2010;59:2817–25.

Background: A recently established hallmark of the pathological alteration of human white adipose tissue (WAT) is fibrosis. The authors aimed to characterize more precisely the composition of subcutaneous (scWAT) and omental WAT (oWAT) fibrosis in obesity. Furthermore, they investigated the relationship of fibrosis with metabolic alterations and surgery-induced weight loss.

Methods: From 65 obese (BMI 48.2 ± 0.8 kg/m²) and 9 lean (BMI 22.8 ± 0.7 kg/m²) subjects, surgical biopsies for scWAT and oWAT were obtained. Obese candidates for bariatric surgery were clinically characterized before, 3, 6, and 12 months after surgery. Additionally, fat mass was evaluated by dual energy X-ray absorptiometry. Quantitative PCR, microscopic observation, and immunohistochemistry were used to quantify and characterize WAT fibrosis.

Results: The authors show a different pattern of fibrous depots and detailed collagen fibers organization in human WAT. Obese subjects had more total fibrosis in oWAT and had more pericellular fibrosis around adipocytes than lean subjects in both depots. Macrophages and mastocytes were highly represented in fibrotic bundles in oWAT, whereas scWAT was more frequently characterized by hypocellular fibrosis. They found a negative relationship between the amount of oWAT fibrosis and adipocyte size as well as triglyceride levels. Notably, scWAT fibrosis correlated negatively with fat mass loss measured at the three time points after surgery.

Conclusion: These data suggest differential clinical consequences of fibrosis in human WAT. Fibrosis in oWAT could contribute to limit adipocyte hypertrophy. In oWAT, fibrosis is associated with a better lipid profile. In scWAT, fibrosis may attenuate fat mass loss induced by surgery.

Divoux et al. have already published several studies on fibrosis of adipose tissue including a review in 2011 [35–37]. Repair of damaged tissue in response to inflammation begins with a regenerative phase where cells are replaced by the same cell type. If damage persists, this phase is followed by a phase of fibrosis accumulation in which normal parenchymal tissue is replaced by connective tissue. Fibrosis is usually characterized by changes in the amount as well as composition of the extracellular matrix (ECM) proteins. During obesity, adipose tissue is inflamed and subsequently undergoes a strong structural remodeling process. ECM is intensely remodeled not only by weight gain [36], but also weight loss [37] which lead Divoux and her team to hypothesize that adipose tissue is a site of fibrous tissue. They showed collagen surrounding adipocytes to be more abundant in obese adipose

tissue (scWAT and oWAT) compared to lean depots. Moreover, they showed that high level of fibrosis in scWAT in patients diminished their fat mass loss after bariatric surgery. Therefore, they suggest that fibrosis is a potential predictive factor for resistance to weight loss in obese patients. In addition, they emphasize that fibrosis should not be neglected in the context of obesity-associated disorders. However, cellular and molecular actors as well as the consequences of fibrosis in WAT have yet to be identified.

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

Overexpression of FTO leads to increased food intake and results in obesity

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Nat Genet 2010;42:1086–92.

Background: Polymorphisms in the first intron of the fat mass and obesity associated (FTO) gene are associated with increased obesity risk. *Fto*-deficient mouse models show a reduction in body mass and body fat content. However, data concerning food intake in animals are controversial. Data about a higher expression of FTO risk alleles in human fibroblasts suggests that an increased FTO expression may be correlated with obesity. To test this hypothesis, the authors compared the effects of different copy numbers of the *Fto* gene in mouse models.

Methods: Mice carrying one (FTO-3) or two (FTO-4) additional copies of the *Fto* gene were generated and were characterized on standard and high-fat diet concerning body measures, energy metabolism and activity.

Results: Transgenic mice exhibited higher body weight as well as elevated fat mass with increasing numbers of *Fto* gene copies after 20 weeks. Also food intake was increased without changes in energy expenditure. No differences in locomotor activity were found between wild-type and transgenic mice. Increased expression of *Fto* leads to increased fat mass and obesity by hyperphagia in this mouse model.

Conclusion: The authors suggest that at-risk SNPs in the human *Fto* gene may enhance FTO expression levels and/or activity. They further suggest that drugs targeting FTO should be designed in order to reduce FTO activity or expression.

Since several genome-wide association (GWA) studies have identified the association between polymorphisms in FTO and obesity risk, the precise physiological function of this gene is still unknown. Mouse models of *Fto* deficiency have already suggested that *Fto* is involved in body weight regulation by interfering with energy expenditure. In this study, an *Fto* overexpression model was created, showing an increased body weight and fat mass, accompanied by elevated plasma triglyceride and fatty acid levels. This was most likely due to a rise in food intake.

This mouse model fits to its counterpart – the *Fto* knockout mouse [38] concerning body weight regulation. In *Fto*-deficient mice, body weight was diminished despite relative hyperphagia and less locomotor activity. Here, *Fto* did not influence these parameters. It would be interesting to study tissue-specific knockout or overexpression in order to identify the tissue and time point where *Fto* influences body weight.

The growth hormone-IGF-1 axis as a mediator for the association between FTO variants and body mass index: results of the Study of Health in Pomerania

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Int J Obes 2011;35:364–72.

Background: Single-nucleotide polymorphisms (SNPs) in the fat mass and obesity associated gene (FTO) are associated with BMI as well as with mortality. It has been speculated that FTO affects most organs concerning their ability to maintain or regenerate proper function when afflicted by various diseases. FTO is ubiquitously expressed, with high expression in the hypothalamus and also in the pituitary gland. It is well known that a decrease in growth hormone (GH) secretion leads to a reduction in lean body mass in older subjects. The authors hypothesize that SNP rs9926289 is associated with insulin-like growth factor (IGF)-1.

Methods: Cross-sectional data from a population-based study in northeastern Germany (Study of Health in Pomerania) were used including 3,882 subjects aged 20–79 years. As outcome measures, BMI, continuous and low IGF-1 according to clinically meaningful age- and gender-specific reference were used.

Results: Statistically significant relationships between FTO and BMI were found over all age groups. Homozygous carriers of the FTO risk allele exhibited lower serum IGF-1 levels adjusted for 5-year age groups, gender and IGF-1-binding protein 3 levels, in subjects below the age of 55 years. FTO genotype effects on BMI were diminished by including IGF-1. In older subjects however, no relationship between FTO and IGF-1 levels were found.

Conclusion: The authors propose that the GH-IGF-1 axis is a mediator for the association between FTO and BMI.

It is now widely accepted that the *FTO* gene is associated with obesity risk and is involved in body weight regulation. In humans, this regulation is mainly due to alterations in food preference and intake [39–41]. However, the molecular pathways for this effect still have to be identified. FTO is highly expressed in central nuclei of the hypothalamus which regulate appetite and also GH secretion. Given the coincidence of high FTO expression in hypothalamic areas which control GH secretion, a potential impact of FTO on the GH-IGF-1 axis is conceivable.

Roszkopf et al. analyzed the association between a new polymorphism in FTO and IGF-1 levels in a German cohort with a high prevalence of overweight and obesity. This polymorphism was also found to be associated with BMI and to be in complete linkage with the first SNP described in FTO [42]. The authors found significantly lower IGF-1 levels in homozygous carriers of the risk allele compared to non-carriers. It has been shown earlier that both over- and underweight are associated with low IGF-1 levels in adults [43]. Adjustment for BMI did not suspend the FTO-IGF-1 association in this study. It seems that a reduction in IGF-1 levels in association with FTO risk alleles contributes to an increased BMI. However, the detailed molecular pathways which are leading to this association are still not clear.

Reduced energy expenditure and impaired feeding-related signals but not high-energy intake reinforces hypothalamic obesity in adults with childhood-onset craniopharyngioma

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J Clin Endocrinol Metab 2010;95:5395–402.

Background: Obesity is frequent in patients with hypothalamic damage due to craniopharyngioma (CP), the most common tumor affecting the hypothalamic-pituitary region in childhood. In the present study, the role of changed energy expenditure, energy intake and attitude towards eating were investigated in adult patients with childhood-onset CP. In addition, association of these measures to the magnitude of hypothalamic damage, due to tumor growth, was investigated.

Methods: 42 adult patients with childhood-onset CP (20 women) aged 28 years (range 17–57) operated between 1958 and 2000 in the South Medical Region of Sweden (population 2.5 million) were studied. Body composition, satiety hormones, basal metabolic rate (indirect calorimetry), physical activity, energy intake, and eating habits were assessed. Comparisons were made with matched controls and between patients with and without tumor growth into the third ventricle (TGTV).

Results: After adjustment for gender and total body weight, patients had a lower basal metabolic rate compared to controls (–90 kcal/24 h; $p = 0.02$). After adjustment for weight, age and gender, energy intake was lower in patients when compared to controls (–430 kcal/24 h; $p = 0.008$). The ratio between energy intake and basal metabolic rate was significantly lower in TGTV patients. Similar dietary macronutrient composition was found, but significantly higher scales in restricting food intake were recorded in patients. In patients, ghrelin levels were lower and insulin and leptin levels were higher ($p < 0.001$) when compared to the controls. Both ghrelin and insulin correlated significantly to tumor growth. Lower levels of physical activity ($p < 0.01$) were recorded in patients.

Conclusions: In patients with childhood-onset CP, the major mechanisms that reinforced the development of obesity were hypothalamic damage causing disrupted or impaired sensitivity to feeding-related signals for leptin, insulin, and ghrelin, and reductions in both basal metabolic rate and physical activity.

Controlling body weight in both children and adults with craniopharyngioma is a true challenge. In the present study, reduced physical activity, in addition to reduced basal metabolic rate, was shown to be an important factor contributing to the positive energy balance in these patients, despite decreased energy intake. These results corroborate the findings from a study performed in children with craniopharyngioma, where reduced physical activity was also determined [44]. The importance of regular and appropriate physical activity in children treated for craniopharyngioma, before the development of disabling obesity, should therefore be acknowledged as an important therapeutic measure, in addition to reduced energy intake, to prevent the development of obesity.

Endocrine disruptors and obesity: an examination of selected persistent organic pollutants in the NHANES 1999–2002 data

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Int J Environ Res Public Health 2010;7:2988–3005.

Background: Endocrine-disrupting chemicals may disrupt endogenous hormonal systems and predispose to weight gain. The aim of the study was to investigate the association between measures of obesity (BMI and WC) and selected persistent organic pollutants (POPs).

Methods: Data from the publicly available cross-sectional National Health and Nutrition Examination Survey (NHANES 99-02) was used. Serum levels of five POPs (1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin, 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin, oxychlorodane, trans-nonchlor and *p,p*-DTT), that were present in 80% of the NHANES population, were determined by high-resolution gas chromatography mass spectrometry. Statistical analysis was performed by various multiple regression models,

with BMI and waist circumference (WC) as outcomes of the models. 2,464 subjects were included for BMI data and 2,448 for WC data analysis.

Results: 1,2,3,4,6,7,8,9-Octachlorodibenzo-*p*-dioxin and DTT were consistently associated with an increase in BMI. A relatively consistent association was also found for 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin with an increase of WC. In addition, several effects of selected POPs were associated with opposite effects depending on gender. Oxychlordane was found to be associated with BMI increase in men and a decrease in women and DTT was associated with WC decrease in man and increase in women.

Conclusions: In this large cross-sectional study, serum levels of several POPs were associated with BMI and WC, making them plausible contributors to obesity epidemic.

Changes in diet and decreased physical activity remain the two main causes of obesity epidemic we are experiencing worldwide. Data from basic and animal studies suggest that environmental chemicals affect the endocrine system as an additional factor. Data from large epidemiological studies on these associations are missing. Two studies, using the large and well-characterized cross-sectional study (National Health and Nutrition Examination Survey) have recently associated two groups of endocrine-disrupting chemicals dioxins and phthalates [45] with obesity. Although the observed effects on both BMI and waist circumference increase were relatively low, it is possible that cumulative effects of these and other endocrine-disrupting chemicals could be more significant. Interestingly, in both studies, certain chemicals had opposite gender-specific effects, adding gender as a further variable in the story. Further prospective studies on the topic are needed.

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