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Hereditary factors and weight loss

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ABSTRACT

Obesity is a chronic disease of multifactorial origin arising from a long-term energy imbalance, in which both genetic and environmental factors may be involved. Obesity is an important cause of morbidity and mortality in developed countries. Implementation of effective strategies in prevention and management of obesity should become a major target in the health care systems worldwide. Weight loss and maintenance depend on the interaction of genetic, metabolic, psychobehavioral and environmental factors. Responsiveness to weight reduction programmes shows a wide interindividual variation and reliable weight loss predictors have not been available.

Major advances have been made recently in the study of genetics of obesity with more than 400 candidate obesity genes being characterized. This paper summarizes available data on the involvement of hereditary factors in weight loss and maintenance. Twin and family studies demonstrated that the weight loss is strongly controlled by genotype. Polymorphisms in several obesity candidate genes was shown to influence the outcome of weight management. However, several studies yield ambiguous results. It should considered that the eating behaviour as a major predictor of weight loss maintenance is also significantly genetically determined.

Weight loss achieved in response to obesity treatment might also be influenced by changes in obesogenic and/or leptogenic genes expression induced by environmental factors such as the type of ingested nutrient and level of physical activity.

More comprehensive studies on interaction between candidate obesity genes, psychobehavioral factors and environmental factors are needed for better understanding the outcome of weight management in our increasingly obesogenic environment.

Key words: obesity, weight loss, weight loss maintenance, obesity candidate genes, gene polymorphisms, gene expression, environmental factors, psychobehavioral factors

STRESZCZENIE

Otyłość jest przewlekłą chorobą, wynikającą z długotrwałej nadwyżki w bilansie energetycznym, spowodowanej wieloma, różnorodnymi czynnikami zarówno genetycznymi, jak i środowiskowymi. Otyłość jest istotną przyczyną chorobowości i śmiertelności w krajach rozwiniętych. Wprowadzenie skutecznych strategii prewencji oraz walki z otyłością powinno być głównym celem opieki zdrowotnej na całym świecie. Utrata, a następnie utrzymanie odpowiedniej masy ciała zależy od wielu, współdziałających ze sobą czynników genetycznych, metabolicznych, psychobehawioralnych i środowiskowych. Odpowiedź na programy powodujące utratę masy ciała świadczy o dużej różnorodności poszczególnych jednostek. Natomiast czynniki predysponujące do utraty masy ciała są nieznane.

Ostatnio nastąpił duży postęp w badaniu genetycznie uwarunkowanej otyłości. Opisano już ponad 400 genów kandydatów otyłości. W niniejszym artykule zebrano dostępne dane na temat dziedzicznych czynników wpływających na utratę i utrzymanie masy ciała. W badaniu przeprowadzonym wśród bliźniaków i ich rodzin udowodniono, że otyłość ściśle wiąże się z genotypem. Na wynik postępowania zmniejszającego masę ciała wpływa polimorfizm kilku genów kandydatów otyłości. Niestety w niektórych dotąd przeprowadzonych badaniach uzyskano dwuznaczne wyniki. Niewątpliwie należy więcej uwagi poświęcić nawykowemu jedzeniu jako głównemu czynnikowi, od którego zależy utrzymanie odpowiedniej masy ciała po schudnięciu co jest także, nawet w znacznym stopniu, uwarunkowane genetycznie.

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Osiągnięcie zmniejszenia masy ciała w czasie leczenia otyłości zależy także od zmian w ekspresji genów powodujących otyłość i leptynę indukowanej różnego rodzaju czynnikami środowiskowymi, takimi jak pożywienie oraz aktywność fizyczna.
Należy przeprowadzić bardziej wnikliwe badania zależności między genami, kandydatami otyłości oraz czynnikami psychobehawioralnymi i środowiskowymi w celu lepszego zrozumienia uzyskiwanych wyników postępowania redukującego masę ciała w coraz bardziej sprzyjającym otyłości otoczeniu.
Słowa kluczowe: otyłość, utrata masy ciała, utrzymanie odpowiedniej masy ciała, geny kandydaci otyłości, polimorfizm genów, ekspresja genów, czynniki środowiskowe, czynniki psychobehawioralne

Over the last decades, the obesity prevalence increased significantly and is becoming a public health problem worldwide in both industrialized and developing countries. In many European countries every fourth or fifth adult is obese. Obesity is a chronic disease of multifactorial origin characterized by enlargement of adipose tissue as a result of an energy surplus caused by a long-term positive energy balance. It origins from the interaction between the external and genetic factors.

Genetic factors versus environmental factors

A question is frequently asked whether the dramatic progression of the obesity epidemic over the last two decades at the turn of the millennium is attributable to genetic predisposition rather than to environmental factors. Since the human genome is unlikely to have undergone important changes over the short period of several decades, the sharp rise in the obesity prevalence cannot be explained by genetic factors.

The 20th century brought not only industrialization and mechanization but also subsequent changes to human lifestyles. The population eating habits have been modified substantially in the countries with increasing obesity prevalence rates. Consumption of fats and simple sugars is increasing while fibre consumption is decreasing. Humans in general, and obese persons in particular, have limited ability to burn fats regardless of their high intake and thus the excessive fat is deposited in the adipose tissue practically without limitation.

Decreased physical activity as a result of low levels of habitual physical activity are another factor implicated in the energy imbalance and the resulting increased prevalence of obesity. Lower physical activity can be ascribed to changes in transport, communications and leisure and to the use of sophisticated technologies and computers both at work and at home. Sedentary work often coupled with sedentary leisure-time activities such as using computers and watching TV, has become a serious public health problem in this regard.

The regulation of body weight and energy homeostasis is subject to complex regulatory mechanisms that maintain balance between energy intake, energy expenditure and energy stores. Genetic factors play an important role in this regulation as well as in development of obesity as reported for both animal models and studies on humans [1]. Based on the current knowledge of the pathogenesis of obesity, the level of involvement of genetic factors in the development of obesity is estimated to be 40–70% [2]. The last edition of the human obesity gene map of 2003 reported more than 400 genes, markers and chromosomal regions to be linked to obesity [3]. Genes influence the regulatory mechanisms involved in control of food intake, perception of hunger and satiety, food preference, food ingestion, nutrient absorption and burning, energy expenditure and nutrient deposition in energy stocks.

Monogenic and polygenic obesities

Recently, several genes could be identified whose mutations led to rare monogenic forms of obesity in humans [4]. Genes for leptin, leptin receptor, proopiomelanocortin (POMC), melanocortin 4 receptor (MC4-R), melanocortin 3 receptor (MC3-R) and the enzyme prohormone convertase 1 (PC1) are among these genes [1]. Nevertheless, mutations of these genes, with the exception of MC4-R, belong to the very rare pathogenetic factors of obesity in humans [5].

The heredity of obesity is due chiefly to interaction of multiple candidate genes found at different locations on the gene map and is therefore polygenic in nature. Candidate obesity genes either predispose to obesity (**obesogenic genes**) or promote leanness (**leptogenic genes**). Genes may interact with each other (gene-gene interactions) or with various environmental factors (gene-environment interactions). Interactions between biological (genes, hormones and neurotransmitters etc.), psychobehavioral and environmental factors affect body fat accumulation and fat distribution as well as obesity related health risks (fig. 1). Such interactions result in a wide range of body weight phenotypes from morbid obesity to asthenic body habitus. In view of this **polygenic heredity** model, an adequate quantification of the involvement of heredity and various candidate genes in obesity development is not feasible.

Association and binding studies indicate links between candidate obesity genes and body weight, body

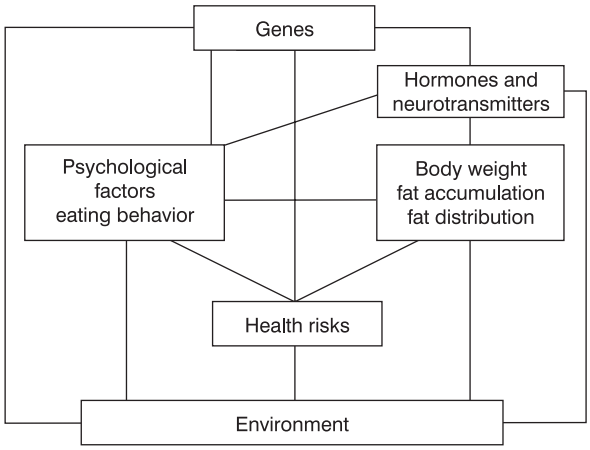

Figure 1. Interactions between biological (genes, hormones and neurotransmitters), psychobehavioral and environmental factors affect body fat accumulation and fat distribution as well as obesity related health risks

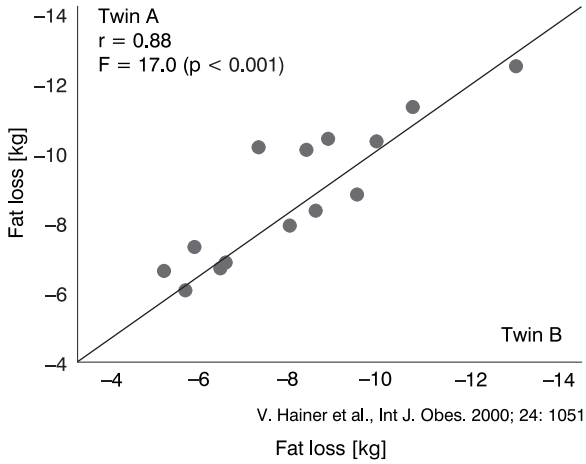

Figure 2. Study conducted in obese female monozygotic twins revealed that intrapair resemblance in VLCD-induced fat loss was 17 times as high as resemblence between pairs

mass index (BMI), body fat distribution and other phenotypic characteristics of obesity including obesity related health risks [3].

Genetic factors affecting body weight loss

With the development of molecular genetics, research currently focuses on the role of genetic factors in body weight loss and maintenance. Studies carried out in monozygotic twins analyze interaction of genetic factors with weight loss programmes. Several studies emphasized the familial aggregation of ability to lose weight. The role of parental obesity in this respect was frequently demonstrated. Other studies dealed with effects of polymorphism of some candidate obesity genes on body weight loss and maintenance. Weight loss maintenance is influenced mainly by psychobehavioral factors that are frequently genetically determined. Finally, many studies analyze the impact of a weight loss intervention (characterized by nutrient intake and type of physical activities) on expression of candidate obesity genes. Variation in expression of obesogenic and leptogenic genes with type of dieting and physical activities may have an effect on efficacy of a weight loss intervention.

Studies on weight loss in monozygotic twins

Studies comparing monozygotic and dizygotic twins were the first to found evidence of the influence of heredity on body weight loss. A study of Stunkard et al. [6] in monozygotic twins revealed genetic factors to be significantly involved in determination of BMI. High correlation of BMI was shown in monozygotic compared to dizygotic twins regardless of whether or not they shared the same environment since birth. A study of Bouchard et al. [7] was focused on responsiveness to a negative energy balance as a result of enhanced physical activities. Weight loss was similar in pairs of identical twins but differed significantly between pairs. Our study [8] revealed significant similarity in weight loss in response to a 1-month weight reduction regimen with a very low energy Redita diet for obese monozygotic twins. Although body weight reduction showed wide interindividual variation, ranging between 5.9 to 12.4 kg, it was similar in pairs of monozygotic twins. Intrapair resemblance in fat loss was 17 times as high as resemblence between pairs (fig. 2). Further analysis of these data revealed a high intra-pair correlation (0.77) for metabolic efficiency [9].

Family background of obesity, ability to oxidize fat and weight loss

In our previous study [10], a high fasting respiratory quotient (RQ) was observed during the treatment by very low calorie diet (VLCD) in obese patients who regained weight at two-year follow-up ("weight regainers") and in those who exhibited repeated cycles of weight loss with a subsequent weight regain ("weight cyclers"). On the other hand, obese patients who succeeded to retain the weight loss initially achieved by the VLCD at 2-year follow-up ("weight losers") or those who did not exhibit weight fluctuations ("weight non-cyclers") were characterized by a significantly lower fasting RQ. A high fasting RQ during the VLCD treatment, which reflects low fat oxidation, should be

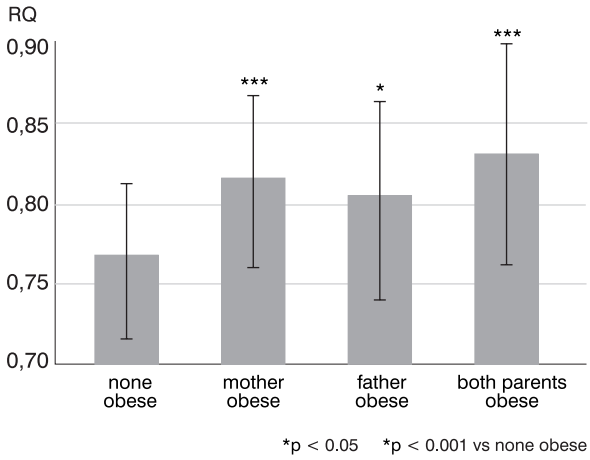

Figure 3. Non-protein respiratory quotient (RQ) in obese subjects categorized according to parental history of obesity (Hainer et al. 2000)

therefore considered as predictor of body weight gain. Obese subjects who reported parental obesity demonstrated significantly higher fasting RQ than those who reported normal weight in both parents (fig. 3). Differences in RQ due to parental obesity remained statistically significant even after adjustment for confounders as body mass index, weight, fat mass, waist circumference, gender, age, average macronutrient intake during the week preceding calorimetry and serum levels of insulin and C-peptide. Obese subjects with both parents obese were found 3.3 times more frequently (42.8% vs. 12.9%) in a cohort in the upper quintile of RQ (low fat oxidizers) than in a cohort in the lower quintile of RQ (high fat oxidizers). In contrast, obese individuals with normal weight parents were revealed much more frequently in the lower quintile of RQ than in the upper quintile of RQ (38.7% vs. 7.1%).

It is evident that an ability to oxidize fat, which affects the outcome of weight reduction programme, is greatly influenced by family background of obesity. Not only fasting RQ but also 24-hr RQ is controlled by familial factors. Toubro et al. [11] revealed that familial membership explained 27% of the variation in 24-hr RQ between individuals. According to Heitmann et al. [12] a high intake of dietary fat is significantly associated with weight gain only among women with parental history of obesity. This susceptibility to weight gain after a high consumption of fat in individuals with parental history of obesity might be due to familial determination of ability to oxidize fat both during fasting and after fat load.

Weight loss in monogenic forms of obesity

Since the monogenic forms of obesity are rather scarce, only few reports on efficacy of the therapy have been available. It can be expected that if the therapy of obesity is targeted on correction of the disorder linked to gene mutation, it should be successful. E.g. obesity due to leptin gene mutation was successfully controlled by administration of recombinant leptin both in adults [13] and children [4]. In view of the known role of genes in the pathogenesis of obesity, some physicians may adopt a nihilist attitude to the treatment of this disorder. Nevertheless, such an approach is unjustified as also shown by the last report on body weight, body fat mass and insulin susceptibility normalization following a 11-month comprehensive weight loss intervention in three children with R236G mutation in the proopiomelanocortin gene [14]. The most common monogenic form of human obesity is that caused by mutations in the gene that encodes melanocortin 4 receptor (MC4-R) [15] and is associated with intensive feeling of hunger and hyperphagia in childhood which decreases with aging. No comprehensive clinical studies on weight loss in patients with MC4-R mutation have been published. However, Butler and Cone [16] described hyperphagia in MC4-R deficient mice fed with a high-fat diet, whereas no hyperphagia was observed when low-fat diet was introduced, thus indicating gene-environment interaction and supporting the role of low-fat diet in weight management even in genetically determined obesities.

Polymorphisms of obesity candidate genes and weight loss

Polymorphisms of several genes have been studied with regard to weight loss and weight loss maintenance in common obesity which is characterized by polygenic heredity (tab. 1).

β3 adrenoreceptor (ADRβ3) plays an important role in adipocyte metabolism as a regulator of catecholamine-induced lipolysis. Among frequent polymorphisms of the ADRβ3 gene is Trp64Arg resulting from the substitution of tryptophane with arginine at locus 64. Some studies focused on the effect of the Trp64Arg polymorphism of the ADRβ3 gene on long-term weight loss regimens. Yoshida et al. [17] found homozygotes for the Arg64 allele to be less successful in reducing weight than Trp64 carriers. Other Japanese studies [18, 19] also confirmed that women with Trp64Arg polymorphism tend to lose weight more slowly when enrolled in a weight loss programme. Shimizu and Mori [20] reported Trp64Arg polymorphism carriers to achieve almost 50% lower weight loss compared to persons with normal β3 adrenoreceptor alleles when given an antiobesity drug mazindol while other studies [21–24]

Table 1. Obesity candidate genes that influence weight loss in weight management programmes

Gene	Polymorphism
Leptin	C-2549A (5´ region)
Leptin receptor	Ser (T) 343 Ser (C)
Serotonin receptor	–759 C/T
Neuromedin β	P73T
PPARγ2	Pro12Ala
ADRβ3	Trp64Arg
UCPs	UCP1 (A-3826G)
	UCP3 promotor (–55C > T)
IRS-1	IRS-1 (Gly972Arg)
CYP 19	11-repeat allele
COMT	Val/Val
PNMT	G-148A
G protein β3 subunit	C825T

PPARγ2 — peroxisome proliferator-activated receptor γ2; ADRβ3 — β3-adrenergic receptor; UCPs — uncoupling proteins; IRS-1 — insulin receptor substrate 1; COMT — catechol-ortho-methyltransferase; CYP 19 — subclass 19 cytochrome P450 aromatase; PNMT — Phenylethanolamin N-methyltransferase

found no difference in weight loss between persons with various polymorphisms of the ADRβ3 gene. Rawson et al. [24] did not reveal any difference in changes to body composition and energy expenditure between the Trp64Arg carriers and non-carriers following weight loss. These discordances could be ascribed to lack of homogeneity of the study groups (obese versus nonobese subjects, diabetics versus nondiabetics) or to ethnic differences. However, a study in Chinese children aged 8–11 years reported a significant body weight decrease in Trp64Arg polymorphism carriers as well [25].

Another study dealt with the effect of the Trp64Arg polymorphism on body fat distribution during weight reduction [26]. Following a three-month weight reduction regimen, Arg64 carriers compared to Arg64 non-carriers showed a lower ratio of visceral to subcutaneous fat, which was particularly true of postmenopausal women. Tchernof et al. [22] and Kim et al. [23] reported visceral fat reduction to be lower in the Arg allele carriers compared to non-carriers after intervention. Benecke et al. [27] described synergism between the β3 adrenoreceptor gene polymorphism (Trp64Arg) and insulin receptor substrate (**IRS**-1) **gene polymorphism** (Gly972Arg) in weight loss control. The coincidence of these two polymorphisms was linked to lower weight loss and higher incidence of type 2 diabetes in obese women following a 13-week weight loss intervention. A question remains unanswered whether the presence of these polymorphisms is one of the major causes of lower weight loss as observed in most diabetics on a weight reduction regimen.

PPARγ2 is an intracellular transcription factor that plays a role in adipogenesis and glucose and lipid homeostasis. A metaanalysis of Pro12Ala polymorphism of the PPARγ2 gene showed positive correlation with BMI. Higher BMI scores were also found in Ala-carriers compared to Ala-non-carriers in a ten-year follow-up study and a three-year follow-up study [28, 29]. Various intervention studies were carried out to elucidate the relationship between the PPARγ2 genotype and weight loss. Lindi et al. [29] reported patients with the Ala12Ala allele to be more successful in reducing body weight than patients with other genotypes. Nevertheless, the study of Nicklas et al. [30] did not find any significant difference in weight loss between the two groups. In our pilot study, we came to the same conclusion [31]. A study of 108 patients followed up for four years on average did not reveal any significant difference in weight loss between carriers and non-carriers of the Ala12 allele of the PPARγ2 gene.

Uncoupling proteins (UCPs) are a family of transmembrane proteins located on the inner mitochondrial membrane. Their function is to uncouple the ATP formation from mitochondrial respiration which results in increased heat formation and higher energy expenditure. Uncoupling protein 1 (UCP1) whose main expression site is brown adipose tissue plays an important role in thermogenesis. Uncoupling protein 2 (UCP2) is similar in structure to uncoupling protein 3 (UCP3), but unlike UCP3 found exclusively in skeletal muscle, it is present in several tissues. Presumably uncoupling proteins play an important role in energy metabolism since they act as transmembrane transporters across the inner mitochondrial membrane in cells. Some studies pointed out correlations between certain UCP gene polymorphisms and resting energy expenditure, physical activity efficacy, substrate oxidation, energy metabolism, BMI, obesity and type 2 diabetes. The role of the UCP1 gene polymorphism in weight loss was revealed by Fumeron et al. [21]. They found the A-3826G polymorphism of the UCP1 gene to be linked to lower weight loss in response to a 25% reduction of energy intake. Harper et al. [32] reported higher UCP3 mRNA expression in persons responsive to dietary intervention compared to those who were resistant to dietary measures.

Leptin. Obese patients whose leptin gene is not mutated often have high leptin levels that may indicate leptin resistance. Leptin administration in these obese patients usually does not promote weight loss. Leptin gene polymorphism in the promotor region 5´ is

linked to lower weight loss in response to low-energy diet [33]. A study focused on the search for weight loss predictors revealed the baseline leptin level (adjusted for age and sex) to be a suitable weight loss predictor in a 2-year cognitive behavioral intervention for obese men [34].

Leptin receptor. Scarce reports on the effect of the leptin receptor gene polymorphism on weight loss in obese persons have been published. Female carriers of the C allele of the leptin receptor gene polymorphism /Ser (T) 343 Ser (C)/ were shown to be more successful in a dietary weight loss intervention [35].

Serotonin receptor. Serotonin is involved in food intake regulation in the central nervous system (CNS) by inducing satiety. The CNS serotonin receptors mediate the effects of serotonin on food intake control. The -759 C/T polymorphism of the 5-HT2C serotonin receptor is linked to lower weight loss in a weight reduction intervention for heterozygotes compared to both of the homozygote types (CC and TT) [36]. Another polymorphism in the gene of the same serotonin receptor is linked to weight loss in adolescent females and seems to be involved in the development of anorexia nervosa [37].

CYP 19 (subclass 19 cytochrome P450 aromatase) and **COMT** (catechol-ortho-methyltransferase). The concomitance of the defined polymorphisms in the genes CYP19 (11-repeat allele) and COMT (Val/Val) leads to more pronounced reduction in BMI and body fat in response to a one-year regular exercise program in overweight and obese postmenopausal women [38].

Genes affecting response to drug treatment of obesity. As mentioned before, the carriers of Trp64Arg **polymorphism of β3 adrenoreceptor** exhibited lower weight loss in response to mazindol treatment [20]. **Phenylethanolamine N-methyltransferase (PNMT)** is an enzyme which plays a major role in catecholamine metabolism and catalyzes the conversion of noradrenalin to adrenalin. The G-148A polymorphism homozygotes showed higher weight loss in a 3-month therapy with a weight loss drug sibutramine [39]. **G-protein β3 subunit** C825T polymorphism influenced differently weight loss in placebo controls and study subjects given a serotonin-noradrenalin reuptake inhibitor sibutramine [40]. The placebo controls with the TT/TC genotypes showed higher weight loss compared to those with the CC genotype. On the other hand, the individuals with the CC genotype achieved higher weight loss in response to sibutramine administration compared to those with the TT/TC genotypes. Studies on drug-induced weight loss provide additional evidence that genotyping could be of relevance in predicting efficacy of antiobesity drugs for obesity treatment.

Eating behaviour and weight loss

It is to be noted that weight loss maintenance clearly depends on the psychobehavioral factors such as the type of eating behaviour. In a recent study we found that the weight loss in response to a one-year weight loss programme including administration of the antiobesity drug sibutramine is significantly associated with decrease in disinhibition scores as assessed by the Eating Inventory [41]. Disinhibition score is a characteristic of the eating behaviour of a person prone to non-compliance with a weight loss regimen and to overeating in response to stress, job and family related problems, increased alcohol intake and depression. Disinhibition scores show a strong hereditary link (heredity rate of 40%) and the gene on chromosome 3, which is most linked to disinhibition, also codes for PPARγ [42]. Based on the most recent study of Bouchard et al. [43], a potential candidate gene determining disinhibition and hunger as eating behaviour factors is a gene on chromosome 15 encoding the hormone neuromedin β, a member of the family of bombesin-like peptides. **Neuromedin β gene polymorphism** (P73T polymorphism T allele homozygote carriers) was linked not only to higher disinhibition and more hunger but also to greater body fat accumulation in their 6-year follow-up study [43].

Effects of the environmental factors on expression of candidate obesity genes

Responsiveness to weight loss intervention may also be modified by effects of environmental factors such as the type of ingested food (e.g., type of nutrient and its character) and level of physical activities on expression of obesogenic and leptogenic genes. Modern molecular genetics provides the possibility to use the microarray method to examine expression of multiple genes in a single adipose tissue specimen. Lopéz et al. [44] examined about 4500 genes in obese rats with cafeteria-diet-induced obesity and their controls. The cafeteria diet induced higher expression of genes involved in fat metabolism regulation and adipocyte differentiation. The highest expression was identified for leptin (*ob*), PPARγ 2 and FABP (Fatty Acid — Binding Protein) genes. Olive oil administration increases expression of thermogenic genes UCP1 and UCP2 in brown adipose tissue and of UCP3 in muscle [45]. Intake of oil with medium-chain triglycerides (MCT), a class of fatty acids, leads to reduction of adipose mass and lower expression of adipogenic genes PPARγ and C/EPB α in rats [46]. UCP1 expression in brown adipose

tissue is stimulated by carotenoids ingested in foods [47]. Nevertheless, our pilot study did not found significant changes to the UCP2 gene expression in subcutaneous adipose tissue for obese women following vitamin A administration [48]. Ribot et al. [49] presume that vitamin A intake correlates with fat accumulation and changes in PPARγ expression. Experimental studies revealed that the type of diet could influence expression of genes controlling food intake. High fat diet decreases serotonin receptor gene expression in the hypothalamus of rats [50].

Expression of candidate obesity genes is influenced not only by diet but also by physical activities [51]. Short-term physical training decreases PPARγ gene expression and at the same time increases gene expression for multiple enzymes involved in fat transport and oxidation in human skeletal muscle [52]. UCP3 expression in human skeletal muscle increases following a single workout but is decreased by endurance training [53].

The fact that both weight loss and maintenance are influenced not only by polymorphisms of candidate obesity genes but also by the level of their expression is suggestive of the need for a comprehensive approach to the study of factors involved in weight loss regulation in weight reduction regimens.

Acknowledgments

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