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Bacteria, viruses, and hypothalamic inflammation: Potential new players in obesity

**Bakterie, wirusy i odczyn zapalny w podwzgórze:
Nowe czynniki w patogenezie otyłości**

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Summary

Being overweight and obese has become an increasingly serious clinical and socioeconomic problem worldwide. The rapidly rising prevalence of obesity has prompted studies on modifiable, causative factors and novel treatment options for this disorder. Recent evidence indicates that excessive weight gain that leads to being overweight and obese may result from alterations in gut microflora. Studies in humans and animals demonstrated that the composition of gut microbiota may differ in lean and obese subjects, suggesting that these differences result in the increased efficiency of caloric extraction from food, enhanced lipogenesis, and impaired central and peripheral regulation of energy balance. Other studies revealed an excessive increase in body weight in a significant percentage of people infected with human adenoviruses SMAM-1 and Ad-36. Dysregulation of adipocyte function by viruses appears to be the most likely cause of excessive fat accumulation in these individuals. Studies on the pathomechanisms related to the pathogenesis of obesity indicated that a high-fat diet triggers the inflammatory response in the hypothalamus, an event that promotes weight gain and further defends elevated body weight through the initiation of central leptin and insulin resistance and impairment of regenerative capacity of hypothalamic neurons. Exposure to a high-calorie diet appears to predispose individuals to obesity not only because of excessive caloric intake but also because of the induction of microbiota- and central inflammatory response-dependent changes that lead to a dysregulation of energy balance.

Key words: **obesity • gut microbiota • adipogenic viruses • hypothalamic inflammation**

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Abbreviations: **Ad** - Human adenovirus; **AMPK** - AMP activated protein kinase; **Angptl4** - angiotensin-like protein-4; **BDV** - Borna disease virus; **BMI** - body mass index; **CCK** - cholecystokinin; **CDV** - Canine distemper virus; **FFAR** - free fatty acid receptors; **Fiaf** - fasting-induced adipose factor; **GLP** - glucagon like peptide; **GPR** - G protein receptor; **IKKa/b** - a kinase of the IKK family; **LBM** - Lean Body Mass; **LPL** - lipoprotein lipase; **LPS** - lipopolysaccharide; **MC4R** - melanocortin receptor-4; **MONICA** - Multinational MONItoring of Trends and Determinants in CArdiovascular Diseases; **NFkb** - nuclear transcription factor; **PYY** - peptide YY; **RAV-7** - Rous type 7 virus; **SCFAs** - short chain fatty acids; **SMAM-1** - Avian adenovirus; **STC1 cells** - an enteroendocrine cell line; **TLR-4** - Toll-like receptor-4; **WC** - waist circumference; **WHR** - waist-to-hip ratio.

INTRODUCTION

Being overweight and obese is a major health problem in both developed countries and the developing world. Both have been recognized by the World Health Organization as a global epidemic in the 21st century. Obesity is generally believed to be the leading public health problem [75]. An estimated 20% of the European population suffers from obesity [34]. In Poland, according to POL-MONICA (Multinational MONItoring of Trends and Determinants in CArdiovascular Diseases) BIS, the prevalence of overweight individuals was 44% for men and 31% for women, and obesity was diagnosed in 28% and 29% of the population, respectively, in 2001 [80]. Obesity has become the growing threat to health and the lives of people worldwide because of considerable morbidity and mortality rates [85]. The most prevalent diseases in civilization, such as type 2 diabetes, hypertension, cardiovascular disease [35], fatty liver disease, and some forms of cancer [40], are known to be the sequelae of obesity. Because of the harmful effects associated with obesity, understanding its etiology is highly important. Obesity is currently considered a pandemic, chronic disease with multiple contributing etiologies. The factors involved in the pathogenesis of obesity include various genetic and non-genetic (e.g., environmental) causes. Renewed interest has been focused on the role of gut microbiota and viral infections in the development of obesity. The importance of hypothalamic inflammation in the etiology of obesity has also been recently highlighted. Therefore, the present study focused on the possible relationship between excessive body weight gain and intestinal flora, viral infections, and diet-induced inflammatory processes in the hypothalamus. Recognizing the etiological factors involved in the development of obesity will allow a better understanding of the mechanisms responsible for the worldwide obesity epidemic and help develop effective treatment methods for this disorder.

CRITERIA FOR OBESITY DIAGNOSIS

Obesity is defined as increased body weight caused by excessive fat accumulation, leading to health impairment. Ideally, the obesity diagnosis should be based on a direct demonstration of an increase in body fat. Various indices, such as body weight, weight and height percentiles, skinfold thickness, percentage of ideal body weight, and body mass index (BMI), have been used to estimate body

fat content [10]. The most recommended and appropriate method to assess body fat percentage and screen for obesity in adults is measuring the BMI. The BMI is a simple index of the weight-for-height ratio, calculated as weight divided by the square of height. It is expressed in metric units (kg/m^2). A BMI between 24.9 and 30.0 kg/m^2 indicates being overweight. A BMI $>30 \text{ kg}/\text{m}^2$ indicates mild obesity. A BMI $>40 \text{ kg}/\text{m}^2$ corresponds to extreme obesity [74]. The BMI, however, does not specify the location and quantity of adipose tissue; therefore, it may be misleading and cause the classification of people who have well-developed muscle mass as being overweight. Conversely, one risk is not identifying obesity in individuals whose fat percentage is considerable but whose BMI does not exceed 30 kg/m^2 [39]. Therefore, other adiposity assessment methods (e.g., measurement of waist circumference [WC], waist-to-hip ratio [WHR; defined as the ratio of waist circumference to hip circumference] [87], and Lean Body Mass [LBM]) [24] are used. Body fat distribution may also be measured using anthropometric methods, such as densitometry or electrical bioimpedance [77]. Accurate data can also be obtained using magnetic resonance imaging or computed tomography, but the costs of these procedures limit their use [77]. Nonetheless, these techniques may provide valuable medical information by allowing researchers and clinicians to distinguish between abdominal visceral fat and subcutaneous fat.

REVIEW OF THE FACTORS INVOLVED IN THE ETIOLOGY OF OBESITY

Obesity, despite the large diversity of causes and complex pathogenesis, in most cases undoubtedly results from long-term positive energy balance. It occurs as a consequence of an inappropriate, high-calorie diet and low physical activity. The modern world allows people to easily access highly processed, energy-rich products, such as fat and sugar, and technical developments have made life easier, thus contributing to low physical activity and reduced energy expenditure. Even a small mismatch between energy intake and expenditure, applied over time, can lead to profound fat accumulation and severe obesity [98]. Moreover, readily available and commonly consumed foods with a high glycemic index are believed to cause overeating [62]. A diet high in fruits and vegetables and low in meat and fat is associated with a lower BMI [100].

The pathogenesis of primary obesity, the most common nutritional disorder, is multifactorial and involves inte-

reactions between metabolic, environmental, psychological, cultural, and genetic factors. The metabolic factors involved in the pathogenesis of obesity include inherited traits that determine energy expenditure (i.e., whole-body fat oxidation rate, basal metabolic rate, and activity of the sympathetic nervous system) [84]. Recent studies showed that psychological factors, such as sleep deprivation, may result in an increase in the incidence of obesity because of a decrease in leptin levels and increase in ghrelin levels, providing a powerful dual signal that the body has an energy deficit and should increase food intake [41,99]. Similarly, chronic stress may enhance appetite through augmented cortisol release and attenuated sex hormone secretion [9]. Social factors include the level of education, socioeconomic status, age, and gender, which have all been shown to affect the vulnerability to obesity [48,63,86]. Several lines of epidemiologic evidence, however, suggest that genetic factors account for up to 80% of a person's predisposition to develop obesity [60]. Genetic factors contribute to three types of obesity: monogenic, syndromic, and common. Monogenic obesity involves cases with a genetic defect that leads to a deficiency of appetite-suppressing hormones (e.g., leptin) or a lack of functional receptors involved in the transmission of satiety signals (e.g., the melanocortin receptor-4 [MC4R]) [36]. Monogenic obesity is a rare disorder, but understanding its pathogenesis allows a detailed comprehension of the mechanisms of appetite control and, in some cases, the use of effective treatments. Syndromic obesity is defined as the co-occurrence of obesity and other inherited developmental and mental abnormalities. The best-known clinical examples of syndromic obesity are Prader-Willi syndrome, Bardet-Biedl syndrome, Alström syndrome, and Cohen syndrome [83]. Common obesity is the result of gene-environment interactions. Some genetic variants are known to be associated with an increased obesity risk [90]. Interestingly, genetic factors that predispose an individual to obesity appear only under certain environmental conditions [78], thus indicating that the environment may change gene expression, likely because of epigenetic modifications [96]. Recently, the factors related to the "internal" environment of the body, such as gut microbiota, have been intensively studied with regard to their effect on energy balance.

HOW CAN GUT MICROFLORA CONTRIBUTE TO OBESITY?

Normal intestinal flora in humans consists of several phyla, including *Firmicutes* and *Bacteroidetes*, accounting for approximately 90% of all microbiota, and *Proteobacteria*, *Fusobacteria*, *Verrucomicrobia*, and *Actinobacteria* [93]. *Firmicutes* contain more than 250 genera, including *Lactobacillus*, *Mycoplasma*, *Bacillus*, and *Clostridium*, and *Bacteroidetes* include approximately 20 genera [8].

Many recently published studies have reported that alterations in gut microbiota may contribute to the development of obesity. Germ-free mice were shown to be resistant to diet-induced obesity [7,82], and the colonization of these animals with normal intestinal flora obtained

from their wildtype counterparts resulted in a rapid increase in body fat content [5], indicating that gut microbiota can be considered a relevant factor in the pathogenesis of obesity. Another study, however, demonstrated that germ-free mice were not protected from excessive weight gain when maintained on a high-fat diet [38]. A specific diet was shown to affect the species composition of intestinal flora. Feeding with a high-fat diet resulted in body weight gain and altered abundance of two main bacterial phyla in the gut in rodents (i.e., a decrease in *Bacteroidetes* and increase in *Firmicutes*) [43,92,103]. Similar changes were found in humans who consumed a high-fat or high-calorie diet [11,47]. Consequently, the obese genotype is associated with an increase in the *Firmicutes/Bacteroidetes* ratio in mice and humans [54,55]. When obese individuals lose weight, the proportion of *Firmicutes* becomes similar to lean individuals [7,54]. Some authors, however, did not confirm the "high *Firmicutes*/low *Bacteroidetes*" hypothesis. They either were not able to demonstrate any significant differences between the composition of gut microbiota in lean and obese individuals [32] or reported an increased occurrence of *Bacteroidetes* in individuals with a high BMI [89].

Gut microbiota have been shown to affect a variety of mechanisms related to digestive tract function, such as the production of vitamins, harvesting energy from the diet, fat storage in the body, the regulation of gastrointestinal hormones, protection from pathogens, and modulation of the inflammatory process in the intestines [16]. When lean, germ-free mice were colonized with microbiota obtained from obese mice, they harvested more energy from food and gained more weight [104], further supporting the hypothesis that gut microbiota in obese animals potentially promotes fat deposition. Bacteria present in the human alimentary tract use indigestible polysaccharides, such as cellulose and resistant starch, as a source of energy. Fermentation of these compounds by bacteria leads to the production of short-chain fatty acids (SCFAs; e.g., acetic acid, propionic acid, and butyric acid). These SCFAs, in turn, may be used by a host organism to produce glucose and lipids (for review, see [90]). Therefore, this biochemical pathway enables the host to utilize additional compounds as nutrients and may be at least partially responsible for weight gain in previously germ-free animals colonized with bacteria. This hypothesis was supported by the discovery that feeding mice a high-fat, high-sugar diet altered the composition of gut microbiota in a way that promoted better carbohydrate utilization [103]. Importantly, similar observations were made in obese humans [104]. *Firmicutes*, whose number increases in obese individuals as stated above, express genes that encode enzymes that break down otherwise indigestible dietary polysaccharides, thus allowing their digestion and absorption and increasing the ability to harvest energy from food [105]. Another explanation of the role of gut microflora in the stimulation of weight gain is a mechanism related to fasting-induced adipose factor (Fiaf), also referred to as angiotensin-like-4 (Angptl4) protein, a member of the angiotensin-like protein family. Angptl4 is a lipoprotein lipase (LPL) inhibitor

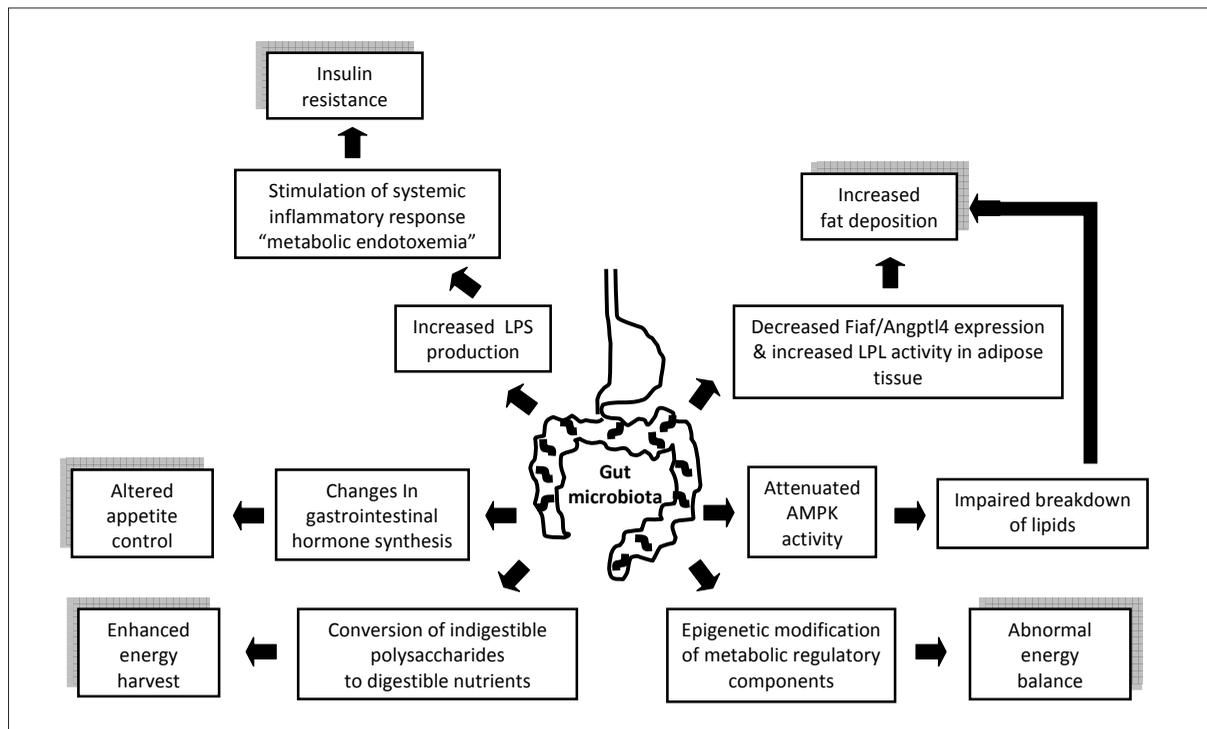


Fig. 1. Mechanisms by which gut microbiota may contribute to the pathogenesis of obesity

and powerful regulator of lipid metabolism [61,94] that is secreted into the blood by different organs. Germ-free mice are characterized by relatively high expression of this protein, but the introduction of microbiota into their body results in the suppression of Angptl4 in the intestinal epithelium [5]. The suppression of Angptl4 results in increased lipase activity in adipose tissue, leading to the enhanced production of lipids and thus contributing to increased fat deposition [5]. Preliminary studies indicated that Angptl4-related mechanisms may also operate in humans [53]. Fat metabolism also depends on the activity of adenosine monophosphate-activated protein kinase (AMPK), which stimulates fatty acid oxidation. The tissue activity of this enzyme is noticeably higher in germ-free mice, likely contributing to mechanisms that protect these animals from diet-induced obesity [4]. Consistent with this, mice maintained on a high-fat diet and treated with antibiotics had higher AMPK activity than before treatment [22].

Recent reports demonstrated that gut bacteria may affect energy balance by initiating the inflammatory process related to increased lipopolysaccharide (LPS) expression. Lipopolysaccharide derived from gut microbiota acts as a trigger for systemic inflammation by binding the CD14 toll-like receptor-4 (TLR-4) complex at the surface of innate immune cells [95]. Thus, LPS stimulates the secretion of proinflammatory cytokines (tumor necrosis factor α and interleukins 1 and 6) and contributes to the development of insulin resistance. Moreover, LPS was shown to link inflammation to metabolic syndrome induced by a high-fat diet [15]. Mice fed a high-fat diet were shown to have plasma LPS concentrations that were markedly

higher than normal, a condition known as “metabolic endotoxemia” [14]. Based on the results of their study, Cani et al. [14] hypothesized that gut microbiota-induced chronic metabolic endotoxemia might be responsible for obesity and decreased insulin sensitivity. Ingestion of a high-fat meal was found to result in endotoxemia, even in lean individuals [33]. The role of intestinal flora in inflammation-dependent positive energy balance that leads to obesity was further supported by the finding that the modulation of gut microbiota by antibiotic treatment or dietary intervention was associated with reduced glucose intolerance, decreased body weight gain, and inflammation inhibition in mice [18,22,64]. Germ-free mice maintained on a high-fat diet did not develop either the intestinal inflammation or obesity that occurred in mice with normal bacterial flora fed a diet rich in fat [30]. Studies in humans have confirmed the validity of the role of LPS in obesity-related metabolic disorders. Specifically, higher LPS concentrations were found in patients with type 2 diabetes compared with patients in the control group who did not present this disorder [25]. Similarly, the blood concentration of another inflammation indicator, C-reactive protein, was recently found to correlate with the *Bacteroidetes/Firmicutes* ratio in obese individuals [108].

The subsequent mechanism by which gut microbiota may affect energy balance is related to changes in gastrointestinal hormones involved in appetite control. The digestive system produces various hormones, such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and cholecystokinin (CCK), which are known to inhibit appetite through an effect on brain feeding centers [26].

Microbiota may indirectly influence the function of enteroendocrine cells through the release of SCFAs that, in turn, bind to the free fatty acid receptors FFAR2 and FFAR3 (also referred to as G-protein receptor 43 [GPR43] and G-protein receptor 41 [GPR41], respectively) in the rat [50], mouse [88], and human [88] intestine. Consistent with this finding, SCFAs were shown to increase the activity of the proglucagon gene and PYY promoter in STC1 cells (i.e., an enteroendocrine cell line) [113] and consequently the secretion of GLP-1 and PYY in mice [57]. Administration of prebiotics (i.e., non-digestive saccharides that enhance microbial fermentation in the gut) resulted in the increased secretion of GLP-1 in rats [49] and GLP-1 and PYY in humans [17]. Germ-free mice had markedly decreased expression of GLP-1, PYY, and CCK in the intestine [31]. Therefore, bacteria that are present in the digestive tract may modify feeding behavior by augmenting satiety signals from the gut. Importantly, together with GLP-1, GLP-2 release was enhanced in rats treated with prebiotics, and this hormonal response may contribute to the inhibition of the inflammatory process in the intestines in obese mice [19]. Moreover, gut microbiota were shown to affect the activity of the endocannabinoid system in mice, indicating that this mechanism may also be involved in the pathogenesis of obesity [70]. A recent hypothesis is that some nutritional patterns in infancy may predispose an individual to obesity in adulthood through a mechanism that involves gut bacteria-derived compounds that affect cell metabolism at the epigenetic level [67]. Collective mechanisms by which gut microbiota may contribute to the pathogenesis of obesity are shown in Fig. 1.

Considering treatments for obesity, nothing can replace a proper diet and physical activity, but manipulation of the gut ecosystem may represent a novel approach for treating obesity and related disorders. The use of various agents that modify gut microflora, such as antibiotics, prebiotics, probiotics (i.e., dietary supplements that contain bacteria with beneficial health effects), and synbiotics (i.e., a mixture of pre- and probiotics), may result in changes in gut microflora that are importantly devoid of side effects and improve health status [46]. However, the diverse mechanisms by which gut microbiota affect metabolism and some discrepancies in research results obtained to date indicate that more research is needed to establish safe and effective methods for the treatment of obesity by manipulating gut bacteria.

VIRAL FACTORS AND OBESITY: WHAT'S NEW?

To date, several viruses associated with the development of obesity have been identified. Their involvement in the pathogenesis of obesity has been reviewed in detail previously [45]. Briefly, canine distemper virus (CDV) [59], Rous type 7 virus (RAV-7) [21], Borna disease virus (BDV) [73], SMAM-1 (avian adenovirus) [29], and scrapie [20] have been linked to abnormal adiposity in animals. Notably, human viruses, such as adenovirus (Ad) 36, Ad-37, and Ad-5, are associated with obesity in animals [2].

Importantly, studies in humans revealed a relationship between infectious pathogens and overweight/obese conditions. For example, herpes simplex viruses have been considered a possible promoter of obesity [37]. Most of the data on the relationships between viral infections and obesity in humans, however, have been generated by studies on adenoviruses. The most important adenoviruses that are implicated in the development of obesity in humans are adenoviruses SMAM-1 and Ad-36. SMAM-1 was the first virus that was shown to cause obesity in humans [29]. Patients who had antibodies against SMAM-1 were characterized by a significantly higher body weight and BMI but, paradoxically, lower serum triglycerides and cholesterol compared with antibody-negative individuals [29]. Further studies reported a significant association between the occurrence of obesity and Ad-36 infection [1,3,58,101,111], although other investigations did not confirm the involvement of Ad-36 in human obesity [12,42].

The pathomechanisms by which viruses might cause obesity have not been fully elucidated. Some animal viruses that are involved in the development of obesity induce fat accumulation caused by alterations in hypothalamic function (for review, see [68]). However, no obvious histopathologic changes in the hypothalamus in Ad-36-infected chickens and mice was demonstrated [28]. Moreover, increased adiposity in virus-infected animals occurred even when no significant changes in food intake were found (for review, see [2]). Therefore, viruses might contribute to the development of obesity through a direct effect on adipose tissue. Indeed, Ad-36 was shown to affect adiposity by upregulating the genes that are crucial for adipocyte differentiation [71,76] and through altered expression of the genes responsible for carbohydrate, lipid, and protein metabolism [110]. Importantly, this virus reduced leptin secretion from adipocytes [107], thus attenuating the most important satiety signal generated by adipose tissue. Moreover, Ad-36 was shown to cause chronic inflammation and promote the development of obesity by increasing the level of monocyte chemoattractant protein-1 [72]. Considering the aforementioned epidemiologic and pathophysiologic data, further investigations are warranted to establish the connections between viral infection and obesity.

CAN DIET CHANGE THE BRAIN? DIET-INDUCED HYPOTHALAMIC INFLAMMATION

A general consensus is that obesity is associated with increased blood levels of inflammatory markers, such as tumor necrosis factor α and interleukins [13]. Circulating cytokines [44] and nutrient excess caused by exposure to fatty acids and glucose in amounts that exceed the demand of the organism [51] activate intracellular inflammatory pathways in various tissues and organs (e.g., liver, muscles, adipocytes, and endothelial cells). A key medical consequence of so-called metabolic inflammation is insulin and leptin resistance [44]. In addition to peripheral inflammation, recently published studies indicate that

overeating may cause similar proinflammatory changes in the hypothalamus, a brain structure that plays a central role in the regulation of food intake. Feeding with a high-fat diet was found to induce inflammation [27] and the apoptosis of neurons in the hypothalamus, events associated with the resistance of hypothalamic neurons to leptin and insulin [69].

Recent studies have focused on the inflammatory response to dietary fat. TLR4 signaling is believed to be the primary mechanism that links the high consumption of dietary fats to the induction of hypothalamic dysfunction that leads to obesity. TLR4 was found to mediate the increased expression of inflammatory cytokines and development of leptin resistance in the hypothalamus in rats fed a high-fat diet or injected intracerebroventricularly with saturated fatty acids [52,66]. TLR4 gene deletion was shown to protect mice against high-fat diet-induced obesity [102]. In peripheral tissues, TLR4 activation stimulates intracellular signaling pathways, including inhibitor of nuclear factor κ -B kinase b (IKKb) and nuclear transcription factor κ b (NF κ b). The former induces the degradation of IKK α , an inhibitor of NF κ b. As a result, activated NF κ b increases the expression of various genes, including those responsible for the immune response. A similar response to chronic exposure to a high-fat diet involves the NF κ b/IKKb pathway, which was recently demonstrated in the rat hypothalamus [109]. The importance of the NF κ b/IKKb pathway in the high-fat diet-induced leptin/insulin resistance of hypothalamic neurons responsible for the control of energy balance was confirmed by other studies [79,112]. In addition to NF κ b/IKKb-induced leptin/insulin insensitivity, the NF κ b/IKKb pathway may cause the dysregulation of hypothalamic feeding centers by impairing autophagy [65]. Autophagy is the self-degradation of cytoplasmic components through lysosomal enzymes and was recently implicated in the control of the activity of hypothalamic neurons that regulate food intake [81,96]. Finally, the NF κ b/IKKb pathway might impair neurogenesis and, thus, reduce the regenerative capacity of hypothalamic neurons involved in food intake control [56]. As mentioned above, prolonged exposure to a high-fat diet was found to enhance the apoptosis of hypothalamic neurons. Such a mechanism, together with impaired neurogenesis, may contribute to irreversible pathological alterations in the hypothalamus. Indeed, switching rats

from a high-fat diet to a standard diet did not decrease the hypothalamic levels of proinflammatory interleukins, despite normalizing caloric intake and reducing body weight [109], suggesting that the inflammatory process was still active 2 months after the change in diet. Therefore, hypothetically, reexposure to a fat-rich diet might cause a return to overfeeding because of maintenance of an unbeneficial proinflammatory state in the hypothalamus, even in subjects who successfully lost weight. Notably, the presence of a local inflammatory process in brain areas responsible for food intake regulation was recently demonstrated in obese humans [23], and a substantial reduction of body weight resulted only in partial reversal of obesity-induced changes in the brain, including the hypothalamus [106].

CONCLUSIONS

Based on the “microbial” and “inflammatory” hypotheses, a high-fat diet may contribute to the pathogenesis of obesity through pathomechanisms of both peripheral and central origin. The former is likely induced by changes in natural intestinal microflora that, in turn, result in the dysregulation of fat metabolism and a blunted gastrointestinal response to food intake. Similarly, viral infections might disturb the differentiation, metabolism, and cytokine response of adipose tissue. Direct dysregulation of brain feeding center function by a local inflammatory process caused by exposure to a diet rich in saturated fatty acids may occur together with the aforementioned systemic disorders, thus resulting in obesity. Understanding the etiology of obesity is important for proper therapeutic and preventive interventions for this rapidly spreading disorder. New studies should focus on probiotic- and prebiotic-induced beneficial changes in gut microbiota, test possible antiviral vaccines or drugs that are able to inhibit the harmful effects of viruses on body metabolism, and investigate the mechanisms and possible treatment modalities that may limit high-fat diet-related neuronal dysfunction.

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REFERENCES

- [1] Almgren M., Atkinson R., He J., Hilding A., Hagman E., Wolk A., Thorell A., Marcus C., Näslund E., Östenson C.G., Schalling M., Lavebratt C.: Adenovirus-36 is associated with obesity in children and adults in Sweden as determined by rapid ELISA. *PLoS One*, 2012; 7: e41652
- [2] Atkinson R.L.: Viruses as an etiology of obesity. *Mayo Clin. Proc.*, 2007; 82: 1192-1198
- [3] Atkinson R.L., Dhurandhar N.V., Allison D.B., Bowen R.L., Israel B.A., Albu J.B., Augustus A.S.: Human adenovirus-36 is associated with increased body weight and paradoxical reduction of serum lipids. *Int. J. Obes.*, 2005; 29: 281-286
- [4] Bäckhed F., Crawford P.A.: Coordinated regulation of the metabolome and lipidome at the host-microbial interface. *Biochim. Biophys. Acta*, 2010; 1801: 240-245
- [5] Bäckhed F., Ding H., Wang T., Hooper L.V., Koh G.Y., Nagy A., Semenkovich C.F., Gordon J.I.: The gut microbiota as an environmental factor that regulates fat storage. *Proc. Natl. Acad. Sci. USA*, 2004; 101: 15718-15723
- [6] Bäckhed F., Ley R.E., Sonnenburg J.L., Peterson D.A., Gordon J.I.: Host-bacterial mutualism in the human intestine. *Science*, 2005; 307: 1915-1920

- [7] Bäckhed F., Manchester J.K., Semenkovich C.F., Gordon J.I.: Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc. Natl. Acad. Sci. USA*, 2007; 104: 979-984
- [8] Bajzer M., Seeley R.J.: Obesity and gut flora. *Nature*, 2006; 444: 1009-1010
- [9] Björntorp P.: Do stress reactions cause abdominal obesity and comorbidities? *Obes. Rev.*, 2001; 2: 73-86
- [10] Boogerd A., Alverdy J., Kumar S., Olson D.L., Schwenk W.F.: Part III. *Obesity. Dis. Mon.*, 2002; 48: 725-742
- [11] Brinkworth G.D., Noakes M., Clifton P.M., Bird A.R.: Comparative effects of very low-carbohydrate, high-fat and high-carbohydrate, low-fat weight-loss diets on bowel habit and faecal short-chain fatty acids and bacterial populations. *Br. J. Nutr.*, 2009; 101: 1493-1502
- [12] Broderick M.P., Hansen C.J., Irvine M., Metzgar D., Campbell K., Baker C., Russell K.L.: Adenovirus 36 seropositivity is strongly associated with race and gender, but not obesity, among US military personnel. *Int. J. Obes.*, 2010; 34: 302-308
- [13] Cai D.: NFκB-mediated metabolic inflammation in peripheral tissues versus central nervous system. *Cell Cycle*, 2009; 8: 2542-2548
- [14] Cani P.D., Amar J., Iglesias M.A., Poggi M., Knauf C., Bastelica D., Neyrinck A.M., Fava F., Tuohy K.M., Chabo C., Waget A., Delmée E., Cousin B., Sulpice T., Chamontin B. et al.: Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*, 2007; 56: 1761-1772
- [15] Cani P.D., Delzenne N.M.: Gut microflora as a target for energy and metabolic homeostasis. *Curr. Opin. Clin. Nutr. Metab. Care*, 2007; 10: 729-734
- [16] Cani P.D., Delzenne N.M.: The gut microbiome as therapeutic target. *Pharmacol. Ther.*, 2011; 130: 202-212
- [17] Cani P.D., Lecourt E., Dewulf E.M., Sohet F.M., Pachikian B.D., Naslain D., De Backer F., Neyrinck A.M., Delzenne N.M.: Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. *Am. J. Clin. Nutr.*, 2009; 90: 1236-1243
- [18] Cani P.D., Neyrinck A.M., Fava F., Knauf C., Burcelin R.G., Tuohy K.M., Gibson G.R., Delzenne N.M.: Selective increases of *bifidobacteria* in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia*, 2007; 50: 2374-2383
- [19] Cani P.D., Possemiers S., Van de Wiele T., Guiot Y., Everard A., Rottier O., Geurts L., Naslain D., Neyrinck A., Lambert D.M., Muccioli G.G., Delzenne N.M.: Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut*, 2009; 58: 1091-1103
- [20] Carp R.I., Callahan S.M., Sersen E.A., Moretz R.C.: Preclinical changes in weight of scrapie-infected mice as a function of scrapie agent-mouse strain combination. *Intervirology*, 1984; 21: 61-69
- [21] Carter J.K., Ow C.L., Smith R.E.: Rous-associated virus type 7 induces a syndrome in chickens characterized by stunting and obesity. *Infect. Immun.*, 1983; 39: 410-422
- [22] Carvalho B.M., Guadagnini D., Tsukumo D.M., Schenka A.A., Latuf-Filho P., Vassallo J., Dias J.C., Kubota L.T., Carvalheira J.B., Saad M.J.: Modulation of gut microbiota by antibiotics improves insulin signalling in high-fat fed mice. *Diabetologia*, 2012; 55: 2823-2834
- [23] Cazettes F., Cohen J.I., Yau P.L., Talbot H., Convit A.: Obesity-mediated inflammation may damage the brain circuit that regulates food intake. *Brain Res.*, 2011; 1373: 101-109
- [24] Cheymol G., Poirier J.M., Carrupt P.A., Testa B., Weissenburger J., Levron J.C., Snoeck E.: Pharmacokinetics of b-adrenoreceptor blockers in obese and normal volunteers. *Br. J. Clin. Pharmacol.*, 1997; 43: 563-570
- [25] Creely S.J., McTernan P.G., Kusminski C.M., Fisher F.M., Da Silva N.F., Khanolkar M., Evans M., Harte A.L., Kumar S.: Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. *Am. J. Physiol. Endocrinol. Metab.*, 2007; 292: E740- E747
- [26] Cummings D.E., Overduin J.: Gastrointestinal regulation of food intake. *J. Clin. Invest.*, 2007; 117: 13-23
- [27] De Souza C.T., Araujo E.P., Bordin S., Ashimine R., Zollner R.L., Boschero A.C., Saad M.J., Velloso L.A.: Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. *Endocrinology*, 2005; 146: 4192-4199
- [28] Dhurandhar N.V., Israel B.A., Kolesar J.M., Mayhew G.F., Cook M.E., Atkinson R.L.: Increased adiposity in animals due to a human virus. *Int. J. Obes. Relat. Metab. Disord.*, 2000; 24: 989-996
- [29] Dhurandhar N.V., Kulkarni P.R., Ajinkya S.M., Sherikar A.A., Atkinson R.L.: Association of adenovirus infection with human obesity. *Obes. Res.*, 1997; 5: 464-469
- [30] Ding S., Chi M.M., Scull B.P., Rigby R., Schwerbrock N.M., Magness S., Jobin C., Lund P.K.: High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. *PLoS One*, 2010; 5: e12191
- [31] Duca F.A., Swartz T.D., Sakar Y., Covasa M.: Increased oral detection, but decreased intestinal signaling for fats in mice lacking gut microbiota. *PLoS One*, 2012; 7: e39748
- [32] Duncan S.H., Lopley G.E., Holtrop G., Ince J., Johnstone A.M., Louis P., Flint H.J.: Human colonic microbiota associated with diet, obesity and weight loss. *Int. J. Obes.*, 2008; 32: 1720-1724
- [33] Erridge C., Attina T., Spickett C.M., Webb D.J.: A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. *Am. J. Clin. Nutr.*, 2007; 86: 1286-1292
- [34] Evans A., Tolonen H., Hense H.W., Ferrario M., Sans S., Kuulasmaa K., WHO MONICA Project: Trends in coronary risk factors in the WHO MONICA project. *Int. J. Epidemiol.*, 2001; 30 (Suppl. 1): S35-S40
- [35] Evans E.M., Rowe D.A., Racette S.B., Ross K.M., McAuley E.: Is the current BMI obesity classification appropriate for black and white postmenopausal women? *Int. J. Obes.*, 2006; 30: 837-843
- [36] Farooqi I.S., O'Rahilly S.: Monogenic obesity in humans. *Annu. Rev. Med.*, 2005; 56: 443-458
- [37] Fernandez-Real J.M., Ferri M.J., Vendrell J., Ricart W.: Burden of infection and fat mass in healthy middle-aged men. *Obesity*, 2007; 15: 245-252
- [38] Fleissner C.K., Huebel N., Abd El-Bary M.M., Loh G., Klaus S., Blaut M.: Absence of intestinal microbiota does not protect mice from diet-induced obesity. *Br. J. Nutr.*, 2010; 104: 919-929
- [39] Franek E.: Postępy patofizjologii otyłości i jej głównych klinicznych skojarzeń. *Med. Metab.*, 2001; 5: 41-54
- [40] Friedman J.M.: Causes and control of excess body fat. *Nature*, 2009; 459: 340-342
- [41] Gangwisch J.E., Malaspina D., Boden-Albala B., Heymsfield S.B.: Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. *Sleep*, 2005; 28: 1289-1296
- [42] Goossens V.J., deJager S.A., Grauls G.E., Gielen M., Vlietinck R.F., Derom C.A., Loos R.J., Rensen S.S., Buurman W.A., Greve J.W., van Baak M.A., Wolfs P.F., Bruggeman C.A., Hoebe C.J.: Lack of evidence for the role of human adenovirus-36 in obesity in a European cohort. *Obesity*, 2011; 19: 220-221
- [43] Hildebrandt M.A., Hoffmann C., Sherrill-Mix S.A., Keilbaugh S.A., Hamady M., Chen Y.Y., Knight R., Ahima R.S., Bushman F., Wu G.D.: High-fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology*, 2009; 137: 1716-1724.e2
- [44] Hotamisligil G.S.: Inflammation and metabolic disorders. *Nature*, 2006; 444: 860-867

- [45] Jaworowska A., Bazylak G.: Infekcje wirusowe w etiologii rozwoju otyłości. *Postępy Hig. Med. Dośw.*, 2006; 60: 227-236
- [46] Jia W., Li H., Zhao L., Nicholson J.K.: Gut microbiota: a potential new territory for drug targeting. *Nat. Rev. Drug Discov.*, 2008; 7: 123-129
- [47] Jumpertz R., Le D.S., Turnbaugh P.J., Trinidad C., Bogardus C., Gordon J.I., Krakoff J.: Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am. J. Clin. Nutr.*, 2011; 94: 58-65
- [48] Kaczmarczyk-Chałas K., Drygas W.: Trendy wysokości, ciężaru ciała i wskaźnika nadwagi wśród dorosłych mieszkańców Łodzi, od 1972 do 1996 roku. *Czynnik Ryzyka*, 2002; 1: 38-43
- [49] Kaji I., Karaki S., Tanaka R., Kuwahara A.: Density distribution of free fatty acid receptor 2 (FFA2)-expressing and GLP-1-producing enteroendocrine L cells in human and rat lower intestine, and increased cell numbers after ingestion of fructo-oligosaccharide. *J. Mol. Histol.*, 2011; 42: 27-38
- [50] Karaki S., Mitsui R., Hayashi H., Kato I., Sugiya H., Iwanaga T., Furness J.B., Kuwahara A.: Short-chain fatty acid receptor, GPR43, is expressed by enteroendocrine cells and mucosal mast cells in rat intestine. *Cell Tissue Res.*, 2006; 324: 353-360
- [51] Kim F., Pham M., Maloney E., Rizzo N.O., Morton G.J., Wisse B.E., Kirk E.A., Chait A., Schwartz M.W.: Vascular inflammation, insulin resistance, and reduced nitric oxide production precede the onset of peripheral insulin resistance. *Arterioscler. Thromb. Vasc. Biol.*, 2008; 28: 1982-1988
- [52] Kleinridders A., Schenten D., Könnner A.C., Belgardt B.F., Mauer J., Okamura T., Wunderlich F.T., Medzhitov R., Brüning J.C.: MyD88 signaling in the CNS is required for development of fatty acid-induced leptin resistance and diet-induced obesity. *Cell Metab.*, 2009; 10: 249-259
- [53] Ley R.E.: Obesity and the human microbiome. *Curr. Opin. Gastroenterol.*, 2010; 26: 5-11
- [54] Ley R.E., Bäckhed F., Turnbaugh P., Lozupone C.A., Knight R.D., Gordon J.I.: Obesity alters gut microbial ecology. *Proc. Natl. Acad. Sci. USA*, 2005; 102: 11070-11075
- [55] Ley R.E., Turnbaugh P.J., Klein S., Gordon J.I.: Human gut microbes associated with obesity. *Nature*, 2006; 444: 1022-1023
- [56] Li J., Tang Y., Cai D.: IKK β /NF- κ B disrupts adult hypothalamic neural stem cells to mediate a neurodegenerative mechanism of dietary obesity and pre-diabetes. *Nat. Cell Biol.*, 2012; 14: 999-1012
- [57] Lin H.V., Frassetto A., Kowalik E.J.Jr., Nawrocki A.R., Lu M.M., Kosinski J.R., Hubert J.A., Szeto D., Yao X., Forrest G., Marsh D.J.: Butyrate and propionate protect against diet-induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. *PLoS One*, 2012; 7: e35240
- [58] Lin W.Y., Dubuisson O., Rubicz R., Liu N., Allison D.B., Curran J.E., Comuzzie A.G., Blangero J., Leach C.T., Göring H., Dhurandhar N.V.: Long-term changes in adiposity and glycemic control are associated with past adenovirus infection. *Diabetes Care*, 2013; 36: 701-707
- [59] Lyons M.J., Faust I.M., Hemmes R.B., Buskirk D.R., Hirsch J., Zabriskie J.B.: A virally induced obesity syndrome in mice. *Science*, 1982; 216: 82-85
- [60] Maes H.H., Neale M.C., Eaves L.J.: Genetic and environmental factors in relative body weight and human adiposity. *Behav. Genet.*, 1997; 27: 325-351
- [61] Mandard S., Zandbergen F., van Straten E., Wahli W., Kuipers F., Müller M., Kersten S.: The fasting-induced adipose factor/angiopoietin-like protein 4 is physically associated with lipoproteins and governs plasma lipid levels and adiposity. *J. Biol. Chem.*, 2006; 281: 934-944
- [62] Martinez J.A.: Body-weight regulation: causes of obesity. *Proc. Nutr. Soc.*, 2000; 49: 337-345
- [63] Mazur E., Małecka-Tendera E., Klimek K.: Czynniki ryzyka otyłości u dzieci szkół podstawowych województwa podkarpackiego Część II. Czynniki ryzyka otyłości u dziewcząt. *Pediatr. Pol.*, 2003; 10: 889-895
- [64] Membrez M., Blancher F., Jaquet M., Bibiloni R., Cani P.D., Burcelin R.G., Corthesy I., Macé K., Chou C.J.: Gut microbiota modulation with norfloxacin and ampicillin enhances glucose tolerance in mice. *FASEB J.*, 2008; 22: 2416-2426
- [65] Meng Q., Cai D.: Defective hypothalamic autophagy directs the central pathogenesis of obesity via the I κ B kinase β (IKK β)/NF- κ B pathway. *J. Biol. Chem.*, 2011; 286: 32324-32332
- [66] Milanski M., Degasperi G., Coope A., Morari J., Denis R., Cintra D.E., Tsukumo D.M., Anhe G., Amaral M.E., Takahashi H.K., Curi R., Oliveira H.C., Carvalheira J.B., Bordin S., Saad M.J., Velloso L.A.: Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. *J. Neurosci.*, 2009; 29: 359-370
- [67] Mischke M., Plösch T.: More than just a gut instinct - the potential interplay between a baby's nutrition, its gut microbiome, and the epigenome. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 2013; 304: R1065-R1069
- [68] Mitra A.K., Clarke K.: Viral obesity: fact or fiction? *Obes. Rev.*, 2010; 11: 289-296
- [69] Moraes J.C., Coope A., Morari J., Cintra D.E., Roman E.A., Pauli J.R., Romanatto T., Carvalheira J.B., Oliveira A.L., Saad M.J., Velloso L.A.: High-fat diet induces apoptosis of hypothalamic neurons. *PLoS One*, 2009; 4: e5045
- [70] Muccioli G.G., Naslain D., Bäckhed F., Reigstad C.S., Lambert D.M., Delzenne N.M., Cani P.D.: The endocannabinoid system links gut microbiota to adipogenesis. *Mol. Syst. Biol.*, 2010; 6: 392
- [71] Na H.N., Kim H., Nam J.H.: Novel genes and cellular pathways related to infection with adenovirus-36 as an obesity agent in human mesenchymal stem cells. *Int. J. Obes.*, 2012; 36: 195-200
- [72] Na H.N., Nam J.H.: Adenovirus 36 as an obesity agent maintains the obesity state by increasing MCP-1 and inducing inflammation. *J. Infect. Dis.*, 2012; 205: 914-922
- [73] Narayan O., Herzog S., Frese K., Scheefers H., Rott R.: Behavioral disease in rats caused by immunopathological responses to persistent borna virus in the brain. *Science*, 1983; 220: 1401-1403
- [74] National Heart Lung and Blood Institute; National Institute of Diabetes and Digestive and Kidney Diseases. Obesity education initiative. In: Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. Bethesda, Md: National Heart, Lung, and Blood Institute in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases; 1998. NIH publication No. 98-4083; 17. <http://www.ncbi.nlm.nih.gov/nlmcatalog/100887711> (25.02.2014)
- [75] Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech. Rep. Ser.*, 2000; 894: 1-253
- [76] Pasarica M., Shin A.C., Yu M., Ou Yang H.M., Rathod M., Jen K.L., MohanKumar S., MohanKumar P.S., Markward N., Dhurandhar N.V.: Human adenovirus 36 induces adiposity, increases insulin sensitivity, and alters hypothalamic monoamines in rats. *Obesity*, 2006; 14: 1905-1913
- [77] Pertyński T., Połać I.: Otyłość u kobiet w okresie pomenopauzalnym. *Menopauza*, 2000; Instytut Centrum Zdrowia Matki Polki, Bibl. Naukowa Tom III: 85-92
- [78] Pi-Sunyer F.X.: The obesity epidemic: pathophysiology and consequences of obesity. *Obes. Res.*, 2002; 10 (Suppl. 2): 97S-104S
- [79] Posey K.A., Clegg D.J., Printz R.L., Byun J., Morton G.J., Vivekanandan-Giri A., Pennathur S., Baskin D.G., Heinecke J.W., Woods S.C., Schwartz M.W., Niswender K.D.: Hypothalamic proinflamma-

- tory lipid accumulation, inflammation, and insulin resistance in rats fed a high-fat diet. *Am. J. Physiol. Endocrinol. Metab.*, 2009; 296: E1003-E1012
- [80] Program POL-MONICA BIS Warszawa. Stan zdrowia ludności Warszawy w roku 2001. Cz. 1. Podstawowe wyniki badania przekrojowego. Biblioteka Kardiologiczna. Warszawa 2002
- [81] Quan W., Kim H.K., Moon E.Y., Kim S.S., Choi C.S., Komatsu M., Jeong Y.T., Lee M.K., Kim K.W., Kim M.S., Lee M.S.: Role of hypothalamic proopiomelanocortin neuron autophagy in the control of appetite and leptin response. *Endocrinology*, 2012; 153: 1817-1826
- [82] Rabot S., Membrez M., Bruneau A., Gérard P., Harach T., Moser M., Raymond F., Mansourian R., Chou C.J.: Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. *FASEB J.*, 2010; 24: 4948-4959
- [83] Rankinen T., Zuberi A., Chagnon Y.C., Weisnagel S.J., Argyropoulos G., Walts B., Pérusse L., Bouchard C.: The human obesity gene map: the 2005 update. *Obesity*, 2006; 14: 529-644
- [84] Ravussin E., Gautier J.F.: Metabolic predictors of weight gain. *Int. J. Obes. Relat. Metab. Disord.*, 1999; 23 (Suppl. 1): 37-41
- [85] Rippe J.M.: The obesity epidemic: challenges and opportunities. *J. Am. Diet. Assoc.*, 1998; 98: S5
- [86] Rohrer J.E., Rohland B.M.: Psychosocial risk factors for obesity among women in a family planning clinic. *BMC Fam. Pract.*, 2004; 5: 20
- [87] Rydén L., Standl E., Bartnik M., Van den Berghe G., Betteridge J., de Boer M.J., Cosentino F., Jönsson B., Laakso M., Malmberg K., Piorri S., Ostergren J., Tuomilehto J., Thrainsdóttir I., Vanhorebeek I. et al.: Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur. Heart J.*, 2007; 28: 88-136
- [88] Samuel B.S., Shaito A., Motoike T., Rey F.E., Backhed F., Manchester J.K., Hammer R.E., Williams S.C., Crowley J., Yanagisawa M., Gordon J.I.: Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc. Natl. Acad. Sci. USA*, 2008; 105: 16767-16772
- [89] Schwirtz A., Taras D., Schäfer K., Beijer S., Bos N.A., Donus C., Hardt P.D.: Microbiota and SCFA in lean and overweight healthy subjects. *Obesity*, 2010; 18: 190-195
- [90] Scott K.P., Gratz S.W., Sheridan P.O., Flint H.J., Duncan S.H.: The influence of diet on the gut microbiota. *Pharmacol. Res.*, 2013; 69: 52-60
- [91] Scuteri A., Sanna S., Chen W.M., Uda M., Albai G., Strait J., Najjar S., Nagaraja R., Orrù M., Usala G., Dei M., Lai S., Maschio A., Busonero F., Mulas A. et al.: Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. *PLoS Genet.*, 2007; 3: e115
- [92] Sefčíková Z., Kmet V., Bujnáková D., Racek L., Mozes S.: Development of gut microflora in obese and lean rats. *Folia Microbiol.*, 2010; 55: 373-375
- [93] Sekirov I., Russell S.L., Antunes L.C., Finlay B.B.: Gut microbiota in health and disease. *Physiol. Rev.*, 2010; 90: 859-904
- [94] Shan L., Yu X.C., Liu Z., Hu Y., Sturgis L.T., Miranda M.L., Liu Q.: The angiotensin-like proteins ANGPTL3 and ANGPTL4 inhibit lipoprotein lipase activity through distinct mechanisms. *J. Biol. Chem.*, 2009; 284: 1419-1424
- [95] Shi H., Kokoeva M.V., Inouye K., Tzameli I., Yin H., Flier J.S.: TLR4 links innate immunity and fatty acid-induced insulin resistance. *J. Clin. Invest.*, 2006; 116: 3015-3025
- [96] Singh R.: Autophagy in the control of food intake. *Adipocyte*, 2012; 1: 75-79
- [97] Slomko H., Heo H.J., Einstein F.H.: Minireview: Epigenetics of obesity and diabetes in humans. *Endocrinology*, 2012; 153: 1025-1030
- [98] Spiegelman B.M., Flier J.S.: Obesity and the regulation of energy balance. *Cell*, 2001; 104: 531-543
- [99] Taheri S., Lin L., Austin D., Young T., Mignot E.: Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med.*, 2004; 1: e62
- [100] Togo P., Osler M., Sorensen T.I., Heitmann B.L.: Food intake patterns and body mass index in observational studies. *Int. J. Obes. Relat. Metab. Disord.*, 2001; 25: 1741-1751
- [101] Trovato G.M., Castro A., Tonzuso A., Garozzo A., Martines G.F., Pirri C., Trovato F., Catalano D.: Human obesity relationship with Ad36 adenovirus and insulin resistance. *Int. J. Obes.*, 2009; 33: 1402-1409
- [102] Tsukumo D.M., Carvalho-Filho M.A., Carvalheira J.B., Prada P.O., Hirabara S.M., Schenka A.A., Araújo E.P., Vassallo J., Curi R., Velloso L.A., Saad M.J.: Loss-of-function mutation in Toll-like receptor 4 prevents diet-induced obesity and insulin resistance. *Diabetes*, 2007; 56: 1986-1998
- [103] Turnbaugh P.J., Backhed F., Fulton L., Gordon J.I.: Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe*, 2008; 3: 213-223
- [104] Turnbaugh P.J., Hamady M., Yatsunenkov T., Cantarel B.L., Duncan A., Ley R.E., Sogin M.L., Jones W.J., Roe B.A., Affourtit J.P., Egholm M., Henrissat B., Heath A.C., Knight R., Gordon J.I.: A core gut microbiome in obese and lean twins. *Nature*, 2009; 457: 480-484
- [105] Turnbaugh P.J., Ley R.E., Mahowald M.A., Magrini V., Mardis E.R., Gordon J.I.: An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*, 2006; 444: 1027-1031
- [106] van de Sande-Lee S., Pereira F.R., Cintra D.E., Fernandes P.T., Cardoso A.R., Garlipp C.R., Chaim E.A., Pareja J.C., Geloneze B., Li L.M., Cendes F., Velloso L.A.: Partial reversibility of hypothalamic dysfunction and changes in brain activity after body mass reduction in obese subjects. *Diabetes*, 2011; 60: 1699-1704
- [107] Vangipuram S.D., Yu M., Tian J., Stanhope K.L., Pasarica M., Havel P.J., Heydari A.R., Dhurandhar N.V.: Adipogenic human adenovirus-36 reduces leptin expression and secretion and increases glucose uptake by fat cells. *Int. J. Obes.*, 2007; 31: 87-96
- [108] Verdam F.J., Fuentes S., de Jonge C., Zoetendal E.G., Erbil R., Greve J.W., Buurman W.A., de Vos W.M., Rensen S.S.: Human intestinal microbiota composition is associated with local and systemic inflammation in obesity. *Obesity*, 2013; 21: E607-E615
- [109] Wang X., Ge A., Cheng M., Guo F., Zhao M., Zhou X., Liu L., Yang N.: Increased hypothalamic inflammation associated with the susceptibility to obesity in rats exposed to high-fat diet. *Exp. Diabetes Res.*, 2012; 2012: 847246
- [110] Wang Z.Q., Yu Y., Zhang X.H., Qin J., Floyd E.: Gene expression profile in human skeletal muscle cells infected with human adenovirus type 36. *J. Med. Virol.*, 2012; 84: 1254-1266
- [111] Yamada T., Hara K., Kadowaki T.: Association of adenovirus 36 infection with obesity and metabolic markers in humans: a meta-analysis of observational studies. *PLoS One*, 2012; 7: e42031
- [112] Zhang X., Zhang G., Zhang H., Karin M., Bai H., Cai D.: Hypothalamic IKK β /NF- κ B and ER stress link overnutrition to energy imbalance and obesity. *Cell*, 2008; 135: 61-73
- [113] Zhou J., Martin R.J., Tulley R.T., Raggio A.M., McCutcheon K.L., Shen L., Danna S.C., Tripathy S., Hegsted M., Keenan M.J.: Dietary resistant starch upregulates total GLP-1 and PYY in a sustained day-long manner through fermentation in rodents. *Am. J. Physiol. Endocrinol. Metab.*, 2008; 295: E1160-E1166

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