REVIEW ARTICLE **(Open Access)**

Gut microbiota - our new important organ

ROSITSA SANDEVA[1], GERGANA SANDEVA[1*], BORISLAVA CHAKAROVA[1], ANELIYA DIMITROVA[2]

[1]Medical Faculty, Trakia University, 6000 Stara Zagora, Bulgaria

[2]Medical University - Pleven, 5800 Pleven, Bulgaria

*Corresponding author; E-mail: geri_sandeva@yahoo.com

Abstract

The term microbiota describes microbial populations which inhabit the body of animals and humans. The microbiota can be regarded as an extra organ (sometimes referred to as the second brain) that contributes unique functions to its host's physiology. This complex organ affects the metabolic balance of the macro-organism by modulating energy absorption, peristalsis, appetite, metabolism of carbohydrates and fats, and fatty deposits in the liver. Short-chain fatty acids derived from fermentation of dietary fiber by anaerobic intestinal microbiota exert multiple beneficial effects on energy metabolism, intestinal permeability and innate immunity. Numerous metabolites that are present in host compartments, such as blood or urine, derive from microbial metabolism or an interplay between host and microbial metabolism. The term microbiome is used to describe the genotypes (the collective genomes of the microbiota) and contains approximately 100-fold more unique genes than the host genome. The distal gut micro-organisms are composed of billions of bacteria and archaea, yeasts and viruses. *Bacteroidetes* and *Firmicutes*, which consist of more than 90% of all phylogenetic types, are the two dominant bacterial divisions in the human and mouse gut. With the emergence of new technologies (real-time PCR), studies about the diseases related with microbiota colonization and the development of treatments against them have gained importance. Regulation of intestinal microbial ecosystem by diet modifications or by using prebiotics or probiotics could reduce intestinal low-grade inflammation and improve gut barrier integrity, thus promoting metabolic balance and weight loss. In this review we summarize available scientific data on gut microbiota - host relationship and the effect of fructose diet on this interaction, as well as intervention strategies against associated metabolic disorders.

Keywords: gut microbiota; microbiome; fructose diet.

1. Introduction

This review examines the data in scientific literature on the interactions between intestinal microbes and host in normal and pathological conditions [11, 35, 37]. In comparisons of distal intestinal microflora of obese and lean humans or animals, most authors found a statistically significant reduction in the relative abundance of *Bacteroidetes* and a significant increase in *Firmicutes* [21, 32]. The link between intestinal microflora and the development of obesity and NAFLD is discussed, as well as the concept of metabolic endotoxemia and the modification of enteroendocrine functions of the intestine and the endocannabinoid system [4, 5, 6, 18, 44]. The present microbial therapies and fecal transplantation for inflammatory and metabolic diseases are examined. Regulating the intestinal microbial ecosystem through diets or using prebiotics or probiotics is a successful guideline aimed at reducing low-level inflammation of the intestine and improving intestinal barrier integrity, thereby affecting the metabolic balance and promoting weight loss [3, 8, 19].

2. Microbiota and microbiome

The microbiota can be regarded as an extra organ of the body that contributes unique functions to host physiology [28, 29]. It plays a role in the regulation of the digestive system, the immunity, and much more [24]. This complex organ affects the metabolic balance of the macro-organism by modulating energy absorption, peristalsis, appetite, metabolism of carbohydrates and fats, and fatty deposits in the liver [13, 15, 40]. Numerous metabolites that are present in host compartments, such as blood or urine, derive from microbial metabolism or an interplay

between host and microbial metabolism [14]. The term microbiome is used to describe the genotypes (the collective genomes) of the microbiota and contains approximately 100-fold more unique genes than the host genome [41].

3. Bacteroidetes and Firmicutes divisions in obesity

The distal gut micro-organisms are composed of billions of bacteria and archaea, yeasts and viruses. *Bacteroidetes* and *Firmicutes*, which consist of more than 90% of all phylogenetic types, are the two dominant bacterial divisions in the human and mouse gut [36]. Comparisons of the distal gut microbiota of obese and lean mice, and those of obese and lean humans revealed a statistically significant reduction in the relative abundance of *Bacteroidetes* and a significantly greater proportion of *Firmicutes* in the obese groups [20]. The BMI of obese and lean pigs are used for the comparative study of microbiota to reduce variables of genotype, diet and environment [16]. The *Bacteroides spp*. is one of the major genera in the *Bacteroidetes* division, and the trends of quantitative changes of both *Bacteroidetes* and *Bacteroides* are similar in obese and lean pigs and their percentages correlate with the body weight. With the emergence of new technologies (real-time PCR), studies about the diseases related with microbiota colonization and the development of treatments against them have gained importance [16]. Recent data suggest that the microbiota can induce obesity through an FXR (farnesoid X receptor)-dependent pathway both by altering the gut microbial composition as well as modulation of FXR signalling in key target tissues such as the liver [43].

4. Microbiota, obesity and NAFLD

A link between the microbiota and development of obesity and NAFLD (non-alcoholic fatty liver disease) has recently been proposed [2, 7, 22, 23]. The major interaction mechanisms between diet, gut microbiota and obesity are shown on Figure 1. High-calorie diet causes obesity and alters gut microbiota, while altered microbiota leads to increased colonic energy harvest, host gene expression and low-grade inflammation which further stimulates obesity.

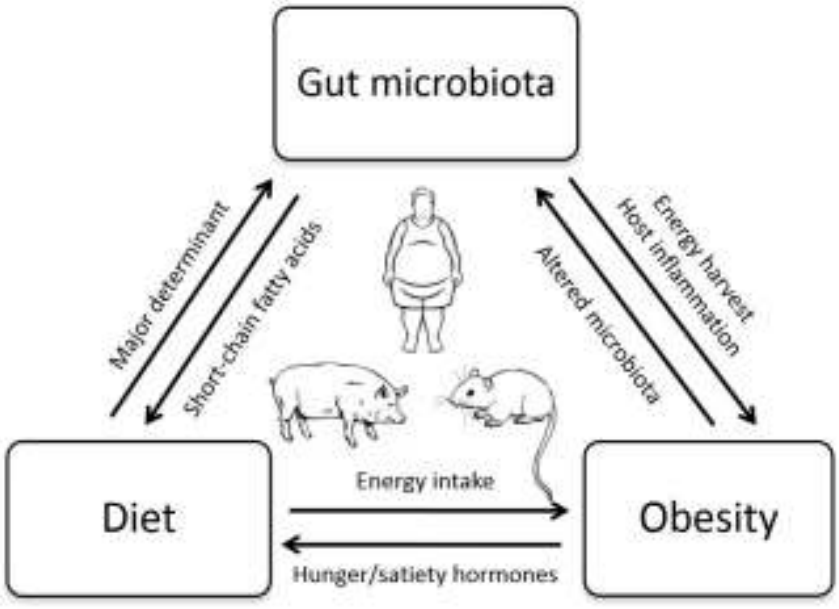

Figure 1. Interactions between gut microbiota, dietary intake and obesity.

First studies in NAFLD are suggesting that microbiota factors are driving forces of hepatic steatosis and inflammation involving certain toll-like receptors and pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNFα) [26]. Obesity induces alterations of gut microbiota, thereby increasing the levels of deoxycholic acid (DCA), a gut bacterial metabolite known to cause DNA damage [42]. Altered intestinal microbiota (dysbiosis) may stimulate hepatic fat deposition through several mechanisms: regulation of gut permeability, increasing low-grade inflammation, modulation of dietary choline metabolism, regulation of bile

acid metabolism and producing endogenous ethanol [17, 39, 44]. In this regard the modulation of gut barrier represent a potential target for novel treatment strategies. The concept of metabolic endotoxemia is one of the triggering factors leading to the development of metabolic inflammation and insulin resistance [34]. Several studies suggest that besides lifestyle and genetic factors an increased permeation of bacterial endotoxin may be involved in the pathogenesis of NAFLD. Patients with different stages of NAFLD suffer from endotoxemia associated with an increased intestinal permeability and a loss of tight junction proteins as well as increased expression of the Toll-like receptors (TLR) and depending signalling cascades in the liver tissue [25]. Figure 2 presents the influence of diet and altered gut microbiota on various host functions in obesity.

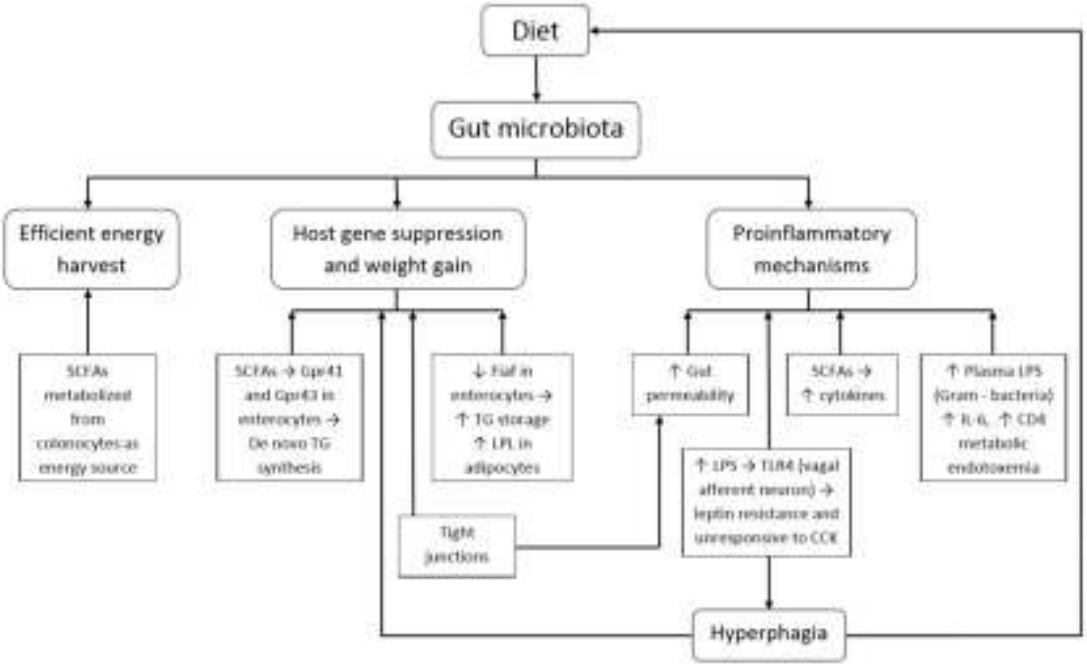

Figure 2. Proposed mechanisms of gut microbiota - obesity relationship. Abbreviations: CCK, cholecystokinin; Fiaf, fasting-induced adiposity factor; Gpr, G-protein coupled receptor; IL-6, interleukin 6; LPL, lipoprotein lipase; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids; TLR4, toll-like receptor - 4.

Backhed et al. found that conventionalization of adult germ-free (GF) C57BL/6 mice with a normal microbiota harvested from cecum of conventionally raised animals produces a 60% increase in body fat content and insulin resistance within 14 days despite reduced food intake. Studies of GF and conventionalized mice revealed that the microbiota promotes absorption of monosaccharides from the gut lumen, with resulting induction of *de novo* hepatic lipogenesis. Fasting-induced adipocyte factor (Fiaf), a member of the angiopoietin-like family of proteins, is selectively suppressed in the intestinal epithelium of normal mice by conventionalization. Analysis of GF and conventionalized, normal and Fiaf knockout mice established that Fiaf is a circulating lipoprotein lipase inhibitor and that its suppression is essential for the microbiota-induced deposition of triglycerides in adipocytes [1]. Although the clear mechanisms involved in the bacteria-host interactions are still under investigation, some researchers found that changes in gut microbiota composition are associated with modification of the enteroendocrine functions of the gut at the level of gut peptides (e.g., GLP-1, GLP-2, PYY, ghrelin) and the endocannabinoid system [4].

5. Diets and intestinal microflora

The composition and functions of the intestinal microflora are particularly dependent on the diet [19, 27, 32]. Results of several human and animals based studies suggest that not only an increased fat and cholesterol intake but also the intake of certain carbohydrates like fructose may be critically associated with the development of NAFLD [31]. It further has been suggest that an increased fructose intake may increase the odds to develop the later stages of the disease (e.g. fibrosis). Other authors suggest that low-dose aspartame consumption

differentially affects gut microbiota-host metabolic interactions in rats [30]. Short-chain fatty acids (SCFAs) derived from fermentation of dietary fibers/polysaccchardies by anaerobic intestinal microbiota exert multiple beneficial effects on energy metabolism, intestinal permeability and innate immunity. Duarte et al. compared the gut microbiomes from obese and lean patients with or without nonalcoholic steatohepatitis (NASH) to outline phenotypic differences. NASH patients showed differences in *Faecalibacterium, Ruminococcus, Lactobacillus* and *Bifidobacterium* abundance compared with the control group. Lean NASH patients had a 3-fold lower abundance of *Faecalibacterium* and *Ruminococcus*, obese NASH patients had high proportion of *Lactobacilli* and overweight NASH patients had reduced *Bifidobacterium* [10]. Continuous exposure to fructose and sugar substitutes may cause dysbiosis with loss of microbial genetic and phylogenic diversity, promoting evolution and maintenance of a Western gut microbiome [33].

6. New microbial therapies

Use of microbial therapies is gaining increasing attention with the success of fecal transplantation in inflammatory and metabolic diseases [9, 38]. The mucus-degrading *Akkermansia muciniphila* has been found to improve the intestinal barrier function in mice on a high fat diet [12]. The butyrate-producing *Eubacterium hallii* was identified via reversed engineering following fecal transplantation in metabolic syndrome. Bacteria belonging to a new genus *Intestinimonas* that are capable of producing butyrate in a novel pathway have great potential to be developed as new therapeutics. The most studied probiotic yeast, *Saccharomyces boulardii*, plays a key role in obesity and associated metabolic disorders. *S. boulardii*-treated mice showed reduced body weight, hepatic steatosis, fat mass and both hepatic and systemic inflammation.

7. Conclusions

Recently obesity has been linked to dysbiosis of the gut microbiota. While diet wields a large influence on body weight, the gut microbiota is integral to the host metabolic response. In obese animals and humans microbiota harvests energy more effectively and may manipulate host gene function. Furthermore, gut microbiota has been shown to play a role in metabolic endotoxemia, the low-grade inflammatory tone linked to obesity and its co-morbidities such as NAFLD, essential hypertension, coronary artery disease, atherosclerosis. Complex multidirectional interactions among diet, the gut microbiota, and obesity have been shown in this review (Figure 1). Potential mechanisms of the relationship between gut microbiota and obesity have been discused, too (Figure 2). Results of several human and animals based studies suggest that high-fat, high-fructose and low-dose aspartame consumption affects gut microbiota-host metabolic interactions. Prebiotics and probiotics act on the diversity of gut microbiota and may have therapeutic potential for obesity. If gut microbiota plays even a minor role in influencing body weight, then there is possibility to manage and prevent obesity through modulation of the gut microbiota. Intentional manipulations of community structure of this extra organ may be useful for regulating energy balance in obese individuals. New treatment strategies will be needed for obesity - this growing worldwide threat to our health.

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