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Review

Glucose metabolism: Focus on gut microbiota, the endocannabinoid system and beyond

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Abstract

The gut microbiota is now considered as a key factor in the regulation of numerous metabolic pathways. Growing evidence suggests that cross-talk between gut bacteria and host is achieved through specific metabolites (such as short-chain fatty acids) and molecular patterns of microbial membranes (lipopolysaccharides) that activate host cell receptors (such as toll-like receptors and G-protein-coupled receptors). The endocannabinoid (eCB) system is an important target in the context of obesity, type 2 diabetes (T2D) and inflammation. It has been demonstrated that eCB system activity is involved in the control of glucose and energy metabolism, and can be tuned up or down by specific gut microbes (for example, *Akkermansia muciniphila*). Numerous studies have also shown that the composition of the gut microbiota differs between obese and/or T2D individuals and those who are lean and non-diabetic. Although some shared taxa are often cited, there is still no clear consensus on the precise microbial composition that triggers metabolic disorders, and causality between specific microbes and the development of such diseases is yet to be proven in humans. Nevertheless, gastric bypass is most likely the most efficient procedure for reducing body weight and treating T2D. Interestingly, several reports have shown that the gut microbiota is profoundly affected by the procedure. It has been suggested that the consistent postoperative increase in certain bacterial groups such as Proteobacteria, Bacteroidetes and Verrucomicrobia (*A. muciniphila*) may explain its beneficial impact in gnotobiotic mice. Taken together, these data suggest that specific gut microbes modulate important host biological systems that contribute to the control of energy homoeostasis, glucose metabolism and inflammation in obesity and T2D.

Keywords: Gut microbiota; Obesity; Endocannabinoid; *Akkermansia*

1. Introduction

The gut microbiota is now considered a separate organ that is involved in the regulation of numerous physiological pathways by impacting different functions of the host [1]. Among these regulatory actions, the influence of gut microbes on energy metabolism is of particular interest, as it has been proposed to be a driving force in the pathogenesis of metabolic diseases, especially obesity. Intestinal microbes have developed a mutually beneficial relationship with their host, and can influence physiological systems by modulating gut motility, intestinal barrier homoeostasis, nutrient absorption and fat distribution [2–4]. The proof of concept for the involvement of gut bacteria in the processes of energy homoeostasis was demonstrated with germ-free mice, which lack microbiota [5]. These animals exhibit a reduced fat mass compared with their conventionally raised littermates in spite of an increased food intake. Moreover, transplantation of faecal microbiota from obese mice into lean germ-free mice has demonstrated the capacity of the bacterial ecosystem to alter host phenotype independently of either genotype or diet [6]. Several studies have confirmed this ability, including a recent one showing that the transplantation of microbiota from twins discordant for obesity partially replicated the donor's phenotype. Transferring gut microbes from obese twin donors to germ-free mice increased their weight gain compared with mice transplanted with microbiota from lean twin donors [7]. These experiments confirm the influence of microbiota on the development of obesity, although causality between the observed changes and metabolic symptoms is still unclear, as well as the applicability of this knowledge to the diagnosis, prevention and treatment of the metabolic syndrome. Nevertheless, they do suggest a relationship between nutrition, gut microbiota and energy homoeostasis.

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The present review discusses recent evidence supporting the hypothesis that gut microbiota can influence the whole of host metabolism through various mechanisms and that changes in microbiota composition can trigger changes in metabolic behaviour. Signalling and molecular pathways involved in the regulation of energy homoeostasis by the gut microbiota are varied [including short-chain fatty acids (SCFAs), the endocannabinoid (eCB) system and gut peptides], with many others that are yet to be identified or clarified.

2. Gut microbiota and metabolism: putative actors and pathways

Among the most studied bacterial metabolites that can interfere with host metabolism are the SCFAs. These products of microbiota-mediated fermentation of polysaccharides modulate levels of several gut hormones involved in glucose and energy homoeostasis, including glucagon-like peptide (GLP)-1 and ghrelin [8,9]. These metabolites circulate in the blood and, thus, can act on peripheral targets to modulate insulin sensitivity and the whole of the host's energy metabolism [10,11]. Unfortunately, most of the pathways underlying these effects are still largely unknown, although several studies have suggested a link with members of a recently identified G-protein-coupled receptor family that includes G-protein-coupled receptors 43 (GPR43) and 41 (GPR41) [12,13]. An elegant study by De Vadder et al. [14] recently showed that SCFAs activate intestinal neoglucogenesis through a cAMP-dependent mechanism and a gut–brain neural circuit involving GPR41, thereby pointing to intestinal neoglucogenesis as a novel actor in gut microbiota ability to host interactions.

In addition to these specific metabolites, the gut bacteria are also able to interact with the host through specific cell membranes and other related molecules that activate pattern-recognition receptors (PRRs). PRRs recognize molecular patterns unique to bacteria and other microorganisms (pathogen-associated molecular patterns, or PAMPs). The most studied PRRs are the toll-like receptors (TLRs) which, when stimulated, result in an inflammatory response, cytokine production and chemokine-mediated recruitment of acute inflammatory cells [15]. Of the PAMPs, we discovered that lipopolysaccharides (LPSs), components of the cell walls of Gram-negative bacteria, contribute to the development of inflammation and insulin resistance in both obesity and type 2 diabetes (T2D) in a condition known as "metabolic endotoxaemia" (Fig. 1) [16,17]. This is associated with altered gut microbiota composition as well as increased intestinal permeability, resulting in increased plasma LPS levels (Fig. 1) [16–19]. Such increases lead to CD14/TLR4 activation, which in turn induces an inflammatory response that results in perturbations of energy homoeostasis as well as increased inflammation, hepatic steatosis, hyperinsulinaemia and insulin resistance [16]. Specifically, LPS acts first on the liver by inducing hepatic insulin resistance [16] and decreasing hepatic inflammatory responses by depleting Kupffer cells prevent high-fat-diet (HFD)-induced metabolic effects [20–22]. Taken together, these data highlight a strong relationship between gut microbiota, inflammation and metabolic perturbations.

There is also growing interest in the study of the intestinal mucus layer and its interactions with microbiota. Recently, we have demonstrated the key role played by the gut microbiota and its interaction with the mucus layer in the context of diet-induced obesity and T2D, where the numbers of *Akkermansia muciniphila*, mucin-degrading bacteria that reside in and abundantly colonize the mucus layer, were negatively correlated with body weight and decreased under HFD conditions (Fig. 1) [23]. Moreover, daily administration of *A. muciniphila* to HFD-induced obese mice for 4 weeks improved their metabolic profile by decreasing weight gain, restoring mucus-layer thickness, and counteracting metabolic endotoxaemia and insulin resistance [23]. A recent study by Shan et al. [24] confirmed that the mucus layer is not only a non-specific physical barrier, but also a complex organized structure that can deliver immunoregulatory signals that participate in gut homoeostasis. On the same topic, Kashyap et al. [25] recently revealed that modification of mucus carbohydrate composition also influences the microbiota. In a gnotobiotic mouse model that presented a severe decrease in mucus fucosylated glycans, they observed a decrease in faecal microbiota diversity compared with a control group that was associated with major changes in faecal and urinary metabolites, suggesting modification of the entire metabolism of the animals [25]. These data were further confirmed by Sommer et al. [26], who found alterations in gut microbiota composition and intestinal architecture in mice with a defect in mucus glycosylation. These findings support an important role for the mucus layer in energy homoeostasis, although the key mechanisms linking intestinal mucus production and whole-body energy homoeostasis have yet to be fully elucidated.

The gut microbiota interact with other organs. Its interactions with the liver through LPS-induced inflammation in obesity have already been alluded to, and other reports strongly suggest interactions with the brain. The presence of cross-talk between the gut microbiota and the brain was demonstrated nearly 10 years ago, when we found that changing the gut microbiota with prebiotics reduced food intake, body weight and fat-mass development in rodents; the phenomenon was also associated with an increase in the endogenous production of anorexigenic peptides, such as GLP-1 and peptide tyrosine tyrosine (PYY), and a decrease in the orexigenic peptide ghrelin [27–29]. Differences in the central expression of peptides involved in energy homoeostasis between germ-free and conventional mice have also been demonstrated [30]. The latter animals exhibited decreased central expression of proglucagon (precursor of GLP-1), and less brain-derived neurotrophic factor (BDNF) and its receptor, compared with the germ-free mice. The authors also found that the expression of food intake regulatory neuropeptides was modified, with decreases in neuropeptide Y (NPY) and Agouti-related peptide (AgRP) expression, and increases in proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) expression compared with conventional mice [30]. These studies suggest the involvement of a neural pathway that allows an exchange of information between gut microbiota and hypothalamic nuclei involved in energy homoeostasis. In