Review

MOLECULAR METABOLISM

How gut microbes talk to organs: The role of endocrine and nervous routes

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ABSTRACT

Background: Changes in gut microbiota composition and activity have been associated with different metabolic disorders, including obesity, diabetes, and cardiometabolic disorders. Recent evidence suggests that different organs are directly under the influence of bacterial metabolites that may directly or indirectly regulate physiological and pathological processes.
Scope of review: We reviewed seminal as well as recent papers showing that gut microbes influence energy, glucose and lipid homeostasis by controlling different metabolic routes such as endocrine, enteric and central nervous system. These dialogues are discussed in the context of obesity and diabetes but also for brain pathologies and neurodegenerative disorders.
Major conclusions: The recent advances in gut microbiota investigation as well as the discovery of specific metabolites interacting with host cells has led to the identification of novel inter-organ communication during metabolic disturbances. This suggests that gut microbes may be viewed as "novel" future therapeutic partners.
This article is part of a special issue on microbiota.

Keywords Gut microbiota; Metabolites; Immune system; Enteric nervous system; Central nervous system; Enteroendocrine cells

1. INTRODUCTION

Our human evolutionary history is a long process that continues to progress. This complex biological evolution also explains the current way we live. We should keep in mind that we are likely the "end product" of a billion years-long process of permanent interaction with our environment. Many evolutionary theories have been proposed and discussed (e.g., Darwinism, creationism), but we have to acknowledge that all current scientific data are largely based on the fact that our environment has played a major role in the way we have evolved. Among the environmental factors, unequivocal evidence shows that microbes have colonized plants, soils and animals. Because microbes colonize many areas of vertebrates (i.e., both outside and inside the body), they have evolved with vertebrates, and they all have established a complex host-microbial relationship, thereby shaping their own genotype and, more importantly, their phenotype. As humans, we are providing them "board and lodging", whereas, in turn, they are conferring on us numerous biological functions that we are unable to perform through our own metabolism. This symbiotic relationship may influence not only our health but also the risk of developing disease when the communication between these "organs" and our organs is disordered.
In this review, we will focus our attention on specific mechanisms by which gut microbes regulate physiological processes in the context of energy and glucose homeostasis. We will discuss how specific "chemical dialogues" may take place between the gut microbiota and target host cells. We will also highlight that this is a bidirectional communication system with a putative impact on host health.

2. GUT MICROBIOTA COMMUNICATION AND GUT PEPTIDES: IMPACT ON HOST METABOLISM

Gut microbiota composition and activity is under the influence of different factors. Among them, specific host-dependent factors, such as genetic background, sex, age, and the immune system, play a key role that is difficult to change on a voluntary basis. Conversely, specific behaviors may directly influence the gut microbiota, such as the use of antibiotics, anti-acid, anti-diabetic, or specific surgical procedures (gastric bypass). Finally, over the last 20 years, numerous data have undoubtedly shown that diet and nutrients strongly contribute to shape

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the gut microbiota composition (e.g., fatty acids, non-digestible carbohydrates, prebiotics, polyphenols) [1—9].

2.1. Microbial metabolites as triggering factors: focus on short-chain fatty acids

Depending on the substrates (amino acids, lipids, carbohydrates) present in the gut lumen, gut bacteria can generate specific metabolites. For example, organic acids such as short-chain fatty acids (SCFAs), or branched-SCFAs and specific bile acid derivatives and vitamins are continuously produced.

The microbial fermentation of carbohydrates in the gut typically produces acetate, propionate, butyrate, and lactate, which are specific SCFAs. The relative proportion of SCFAs and, eventually, their relative abundance and ratio may result in a specific host response. It is important to note that this metabolic collaboration is dependent on the presence of a particular genus of bacteria because all substrates (nutrients) are not equally transformed into SCFAs upon carbohydrate fermentation. In addition, not all the SCFAs have the same metabolic impact. For example, butyrate is known to be a primary energy source for colonocytes [10,11]. Acetate is in theory used as a cholesterol or fatty acid precursor, whereas propionate is gluconeogenic in the liver and the gut, but it may also neutralize lipogenesis from acetate or glucose in the liver [12,13].

In addition to this direct role in the de novo production of nutrients, it also has been demonstrated that these SCFAs can bind to specific receptors, such as G-protein coupled receptors FFAR2 and FFAR3, (also called GPR43 and 41). These two receptors are structurally related to each other and activated by SCFAs. More than a decade ago, Brown et al. identified the endogenous ligand of these receptors [14]. They are encoded by genes that are located close to each other in the genome. Moreover, these receptors exhibit some overlapping expression but also partially share signaling pathways ($G\alpha_{i/o}$ and/or G_q). Thus, for example, the stimulation of GPR43 by SCFAs reduces cAMP production and activates ERK (extracellular signal-regulated kinase) cascade via $G\alpha_{i/o}$ dependent mechanism, or increases intracellular Ca^{2+} levels and promotes activation of MAPK pathway (mitogen-activated protein kinase) via interactions with the G_q family. Since this finding, numerous reports have shown that these receptors are expressed in a wide variety of tissues and cells types (immune cells, endocrine cells and adipocytes) [15,16]. For example, GPR43 mRNA is expressed in white adipose tissues as well as in cellular models (e.g., 3T3-L1 differentiated in adipocyte and mature adipocytes). In addition, several studies have shown that GPR43 is highly expressed in the adipose tissue during high-fat diet (HFD)-induced obesity compared with control normal chow diet-fed mice [17—19]. SCFAs are also able to suppress cAMP-induced lipolysis (isoproterenol) in a concentration dependent manner [17]. By using GPR43 knockout mice, Ge and colleagues found that this is an effect dependent on GPR43 [20]. SCFAs also have been shown to be involved in the management of inflammation, by mechanisms comprising the control of neutrophil chemotaxis but also by acting on the proliferation of T regulatory cells (Treg) [21,22]. For example, different reports show that GPR43 contribute to the recruitment of immune cells and their activity may impact on the regulation of inflammatory processes in intestinal inflammation [23].

More recently, De Vadder and colleagues have shown that gut microbes improve various features of energy metabolism (e.g., insulin sensitivity) via mechanisms depending of a SCFAs-induced intestinal gluconeogenesis in the intestine. Specifically, they found that propionate acts on GPR43 in the periportal afferent neural system to induce intestinal gluconeogenesis via a gut-brain neural circuit and, eventually, has beneficial effects on host physiology [13].

Because, the bacterial fermentation of dietary fibers in the intestine is the major source of the SCFAs, these discoveries have led to the unequivocal demonstration of molecular mechanisms by which gut microbes dialog with organs and contribute to control host metabolism through the regulation of several intracellular cascades. Hence, SCFAs are considered to be key messengers through which bacteria are able to talk to organs and thereby modulate host metabolism.

2.2. Gut microbes may control food intake

Over the last 15 years, different researchers have contributed to decoding the mechanisms explaining how the ingestion of non-digestible carbohydrates (e.g., inulin-type fructans, arabinoxylans, chitin glucan, resistant starches) improves metabolic disorders through a gut microbiota-dependent pathway [24—26]. In 2004, it was reported that changing the gut microbiota in rats using three different prebiotics (inulin-type fructans) that varied according to their chemical structure reduced food intake, body weight, and fat mass [24]. This discovery raised key questions: how can we explain that changing the gut microbes by using prebiotics affects the control of a brain-controlled factors such as food intake? Are there any other putative factors involved? These questions will be addressed in a different part of this review.

2.3. Gut microbes and gut peptides

Searching for a mechanism of action, we reasoned that because the vast majority of microbes residing in the gut are located in the ileum and in the colon, the beneficial effects of prebiotics might be related to this area of the gastro-intestinal tract. Interestingly, this portion of the intestine is precisely where most of the enteroendocrine L-cells are located. Because L-cells produce anorexigenic peptides such as glucagon-like peptide-1 (GLP-1) and Peptide YY (PYY), we decided to quantify the concentration of these peptides in the portal vein of rodents in which the microbial composition was changed by using prebiotics. We discovered that the levels of GLP-1 and PYY were increased in portal vein blood [24,27]. This effect was associated with an increase in the GLP-1 and PYY precursors (preproglucagon and preproPYYmRNA expression, respectively) in the ileum and in the colon. We next discovered that affecting the gut microbiota composition and activity strongly decreased the orexigenic hormone ghrelin in the blood of rats treated with prebiotics [24] (Figure 1).

These observations were the first linking gut microbiota activity, and hence a phenomenon occurring in the lower part of the gut, with signals integrated into the brain to control food intake. Most of these findings have been confirmed with different non-digestible carbohydrates (i.e., resistant starches and arabinoxylans) and will not be discussed in the present review [28—34].

Interestingly, prebiotic (inulin-type fructans) fermentation increased the abundance of SCFAs (i.e., propionate and butyrate) [35,36]. GPR41 and 43 are expressed on enteroendocrine L-cells producing GLP-1 and PYY [37]. As discussed earlier in this review, SCFAs are ligands for these receptors. Therefore, it is easy to consider that SCFA activation of both GPR's promotes the secretion of GLP-1 and peptide YY, as shown by several reports [37—39].

To further investigate whether the beneficial effects observed between changes in gut microbes and metabolism were explained by a mechanism involving GLP-1 production, Cani et al. have used two different approaches. They first used genetic and pharmacological manipulations and found that mice lacking the GLP-1 receptor (GLP-1R) were not sensitive to the impact of prebiotics [40]. In other words, in the absence of GLP-1R, mice remained obese, resistant to insulin, and did not reduce their food intake. The same observation was made

