REVIEW

Gut-brain signaling in energy homeostasis: the unexpected role of microbiota-derived succinate

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Abstract

In the context of the obesity epidemic, dietary fibers that are found essentially in fruit and vegetables attract more and more attention, since they exert numerous metabolic benefits resulting in the moderation of body weight. Short-chain fatty acids, such as propionate and butyrate, produced through their fermentation by the intestinal microbiota, have long been thought to be the mediators of these benefits. In fact, propionate and butyrate were recently shown to activate intestinal gluconeogenesis, a function exerting metabolic benefits via its capacity of signaling to the brain by gastrointestinal nerves. Recently, succinate, the precursor of propionate in the bacterial metabolism, has also been shown to exert signaling properties, including the activation of intestinal gluconeogenesis.

Key Words

- gut microbiota
- succinate
- short-chain fatty acid
- intestinal gluconeogenesis
- gut–brain axis
- glucose metabolism

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Introduction

The worldwide increase in obesity and associated illnesses such as type 2 diabetes has urged the scientific community to improve our understanding of the mechanisms underlying energy homeostasis. A well-documented area relates to the hormonal signals that the gut releases in blood in response to nutrient assimilation and which modulate hunger sensations and glucose homeostasis, such as cholecystokinin and glucagon-like peptide 1, a set of processes referred to as the gut–brain axis. An increasingly popular field of investigation relates to the gut microbiota, residing mainly in the distal gut. The genetic composition of the gut microbiota is altered in obesity and metabolic diseases, which has led to the idea that the microbiota changes could have a role in the regulation of host metabolism. It is noteworthy that various macronutrients, such as dietary protein, are also able to influence the host metabolism, and especially hunger and glucose control. In this context, the possible role of dietary fiber, via its fermentation by the gut microbiota, currently attracts more and more interest.

Effects of dietary fiber on microbiota and host metabolism

Dietary fiber corresponds to oligosaccharides that cannot be metabolized by the host intestinal enzymes, but are metabolized by the microbiota in the cecum and colon (Macfarlane & Macfarlane 2003). The major products from the microbial fermentation are short-chain fatty acids (SCFAs), namely acetate, propionate and butyrate (Cummings *et al.* 1987). These metabolites can then be efficiently used by the intestinal mucosa and/or next host metabolism. The concentration of SCFAs varies along the length of the gut, with the highest concentrations in the proximal colon. For a thorough review on SCFA

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production and physiological concentrations refer to study by Koh and coworkers (Koh *et al.* 2016).

Among dietary fiber, fructans (or fructo-oligosaccharides, FOS) have been studied extensively. Some bacteria, such as *Bifidobacterium* spp., express the enzyme β-fructofuranosidase and are able to break down the oligosaccharides. The presence of FOS in the intestine stimulates the development of such bacteria. For example, a remarkable increase in *Bifidobacterium* spp. was observed in diabetic mice that were fed inulin-type fructans (Cani *et al.* 2007, 2009, Dewulf *et al.* 2011). The increase in Bifidobacteria was inversely correlated to the development of adiposity and glucose intolerance (Cani *et al.* 2007). Moreover, fructan supplementation induces an increase of GLP-1-producing L-cells in the colon and jejunum, which could be at the origin of the metabolic benefits linked to GLP-1 (Cani *et al.* 2006, Delzenne *et al.* 2007).

Short-chain fatty acids are a link in the metabolic benefits of dietary fiber

It has long been thought that the production of SCFAs from dietary fiber by the gut microbiota could account for the beneficial effects of dietary fiber (for a review, see Koh *et al.* 2016). For instance, mice and rats fed a butyrate-enriched diet have increased thermogenesis and energy expenditure (Gao *et al.* 2009), as well as improved glucose tolerance (Lin *et al.* 2012, De Vadder *et al.* 2014). Human studies using acute and long-term administration of the inulin-propionate ester, which can be metabolized to propionate in the colon, have shown that GLP-1 and PYY secretion were increased, concomitantly with reduced calorie intake and weight gain (Chambers *et al.* 2015).

Besides, we previously showed that the delivery of glucose in the portal vein and its neural sensing by the sodium-coupled glucose co-transporter 3 (SGLT3) in the vein walls and subsequent signaling to the brain initiates a set of events, generally referred to as the 'portal glucose signal'. This signal promotes various metabolic benefits, including decreased food intake and improved insulin sensitivity and glucose control (Delaere *et al.* 2012, see e.g. Soty *et al.* 2017 for a review). We also established that intestinal gluconeogenesis (IGN), a gut function-releasing glucose upstream of the portal nervous system, could activate the portal glucose signal and its associated benefits (Mithieux *et al.* 2005, Troy *et al.* 2008). It is noteworthy that we could then show that the activation of IGN by butyrate and propionate could in fact account for by the beneficial metabolic effects of dietary fibers (De Vadder *et al.* 2014). This provided a key mechanistic insight in the way by which the microbiota function may influence host metabolism.

Microbiota-derived succinate

Succinate is a major intermediary in the citric acid cycle, where it stands between succinyl-coA and fumarate. In the gut, the microbiota can also produce important amounts of succinate, especially from fermentation of polysaccharides and oligosaccharides. Microbiota-produced succinate is classically described as an intermediate in propionate synthesis and is supposed to accumulate to a lesser extent because of its conversion in propionate (Cummings *et al.* 1987). However, a marked increase in cecal succinate concentration was reported upon dietary fiber feeding in mice (De Vadder *et al.* 2016). Human studies have shown that succinate ranges in a concentration from 1 to 3 mM in intestinal content and feces, i.e. 2–4% of total organic anions in feces (Meijer-Severs & van Santen 1987). In mice, its cecal concentration is greatly increased by feeding dietary fiber, especially whether fiber is given in supplementation of a high-fat diet (Jakobsdottir *et al.* 2013, Everard *et al.* 2014, Zhong *et al.* 2015, De Vadder *et al.* 2016). The major producers of succinate in the gut are bacteria from the phylum Bacteroidetes (Miller & Wolin 1979). Succinate has been shown to activate dendritic cells (Rubic *et al.* 2008), thus acting as a modulator of intestinal inflammation. In line with this idea, an increase in succinate, induced by a diet rich in polyphenols, blocks growth and proliferation of colon cancer cells, as well as angiogenesis (Haraguchi *et al.* 2014). Furthermore, colonization of conventionally raised mice with the succinate-producing bacterium *Prevotella copri* contributes to an improvement in glucose control, through succinate-dependent and -independent mechanisms (Kovatcheva-Datchary *et al.* 2015, De Vadder *et al.* 2016).

A putative receptor for succinate was discovered in 2004, named GPR91 (He *et al.* 2004). While *in vitro* and *in silico* studies have suggested that GPR91 can also bind other carboxylic acids, its affinity for them was much lower than that for succinate (EC_{50} from 20 to 50 µM), suggesting that succinate is the endogenous ligand of GPR91. While GPR91 is widely expressed in the body, plasma concentrations of succinate vary from 2 to 20 µM in mice and humans (Kushnir *et al.* 2001, Sadagopan *et al.* 2007), suggesting that, under physiological conditions, activation of GPR91 by succinate might only be relevant in the gut lumen.

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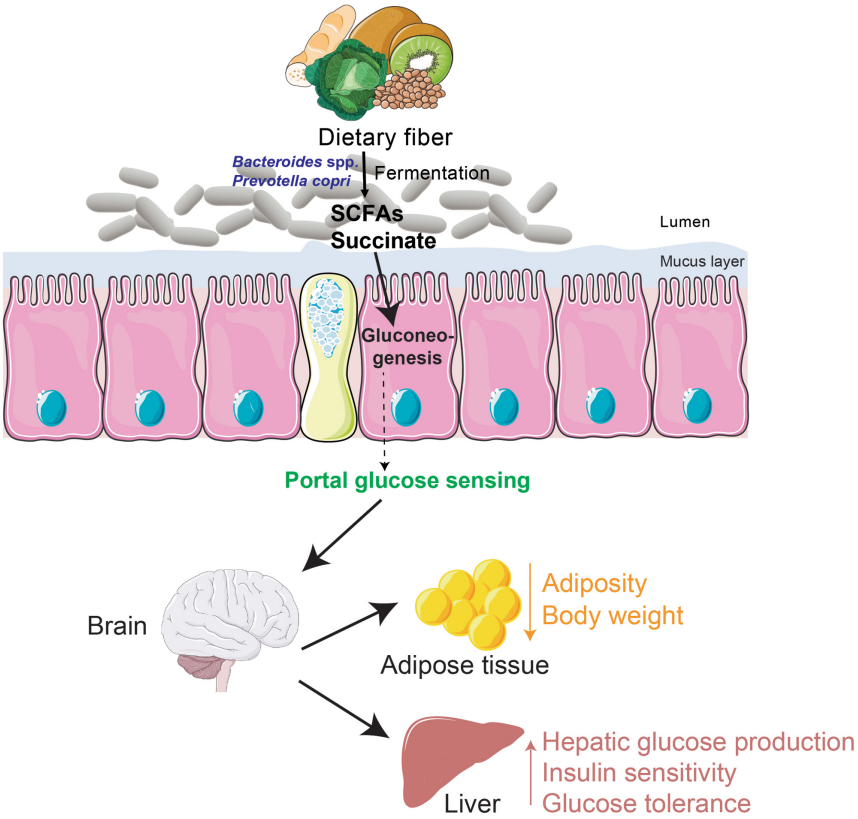

Figure 1
Sequence of events accounting for the metabolic benefits of dietary fiber on host metabolism.

Succinate signaling to the brain: intestinal gluconeogenesis as a crucial link

It is noteworthy that both propionate and succinate were previously described as efficient substrates for glucose production in the liver. This raised the hypothesis that, under *in vivo* conditions, succinate could be converted to glucose by the intestine, just as we previously showed for propionate (De Vadder *et al.* 2014). In fact, we showed that succinate produced from dietary fiber, as propionate, initiates the glucose signal to the brain and its metabolic benefits (Fig. 1), instead of reaching the liver to increase hepatic glucose production and peripheral glycemia.

Interestingly, while fiber feeding induced a shift in microbiota composition with an increase in Bacteroidetes and decrease in Firmicutes (David *et al.* 2014, De Vadder *et al.* 2014, 2016, Kovatcheva-Datchary *et al.* 2015); this was not the explanation of the metabolic benefits conferred on the host by fibers. Instead, the mechanisms explaining the benefits of fiber implied the aforementioned dialog with the host intestinal metabolism, resulting in the activation of IGN and its capacity of signaling to the brain. Accordingly, mice with an intestine-specific knockout of the *G6pc* gene (the major gene involved in glucose production) still exhibited an overweight and glucose-intolerant phenotype when fed a high-fat diet in conjunction with fiber or succinate (De Vadder *et al.* 2014, 2016). Interestingly, this phenotype was observed despite changes in the microbiota composition similar to those in their wild-type counterparts. Therefore, it is the capacity of the host to use bacterial metabolites (especially propionate and succinate) to activate gut–brain glucose signaling and not the changes in microbiota composition, that drives the metabolic benefits of SCFAs and succinate.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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