Colonic acetate in obesity: location matters!

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Abstract
Gut micro-organisms are recognized as crucial regulators of host immunity and the microbiota has been implicated in several inflammatory, immune, inflammatory or even psychiatric disorders. Therefore the analysis of the complex interactions between gut microbiota and the host is currently under intense investigation. Most of our knowledge stems from the study of animal models while translational research and data in humans are necessary to move the field forward and to evolve to diagnostic and therapeutic application. Amongst the microbial by-products, short chain fatty acids such as acetate yielded by fermentation of non-digestible fibers, were pointed as metabolic modulators. Here we highlight a study evaluating the effects of colonic infusion of one of the short chain fatty acids, acetate, in a cohort of overweight and obese normoglycaemic subjects.

Key words: dietary fibres, fat oxidation, gut microbiota, insulin sensitivity, PYY.

INTRODUCTION
The gut microbiota collectively represents around 40 trillion micro-organisms living in the gut and is nowadays considered a crucial regulator of host immunity and metabolism [1]. Alterations of the gut microbiota are associated with the occurrence and/or evolution of several metabolic, inflammatory and immune diseases, such as obesity, diabetes, inflammatory bowel diseases, asthma and allergies [2]. More than two decades of research have now been devoted to the understanding of the mechanisms underlying the impact of gut microbes on their host and the exploitation of the recruited pathways to preventive and therapeutic ends. Among the microbial by-products involved in the gut microbiota–host cross-talk, short-chain fatty acids (SCFAs) have received much of the attention [3,4]. SCFAs such as acetate, propionate and butyrate are produced by microbial fermentation of non-digestible foods such as dietary fibres. They can interact with host tissues by modulating the activity of histone deacetylases and activating G-protein-coupled receptors such as GPR43 [5].

Much of our knowledge on SCFAs arises from rodent experiments, whereas translational research performed in human subjects remains an exception [4]. However, gathering data in humans is essential to validate findings from rodent experiments and to move toward clinical applications. In this issue of Clinical Science, van der Beek et al. [6] present the results of a pilot study in which they investigated the impact of a colonic infusion of acetate in overweight and obese normoglycaemic men. They showed that distal colonic acetate infusion beneficially affects whole-body substrate metabolism via an increase in fat oxidation and anorexic peptide YY (PYY) levels. Interestingly, their data highlighted that the site of delivery (distal rather than proximal) influences the benefits conferred by acetate infusion. Besides pinpointing information valuable for the design of future studies, a major interest of the work relies on the fact that the study investigated experimentally the metabolic impact of acetate in humans, rather than performing, as is more commonly seen, correlational analyses between SCFAs and metabolic markers.

ACETATE, FRIEND OR FOE?
If and how acetate confers metabolic benefits on the host is vigorously debated and fosters active research in the field [4,7,8]. In mice, colonic acetate has been shown to induce the secretion of glucagon-like peptide (GLP)-1, a satiety gut hormone [9], to reduce food intake [10] and to protect against diet-induced obesity and insulin resistance [11,12]. Perry et al. [13] proposed recently that circulating acetate rather enhances insulin secretion through a microbiome–brain–β-cell axis, a process that, in the face of chronic exposure to calorically dense and abundant food, promotes obesity and the metabolic syndrome. Contrasting with

Abbreviations: DP, degree of polymerization; GPR, G-protein-coupled receptor; PYY, peptide YY; SCFA, short-chain fatty acid.
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these observations, Lin et al. [11] found no effect of acetate on gut hormone levels after an acute challenge or on food intake in a 9-day study.

Most data on acetate derive from animal and in vitro studies (reviewed by Canfora et al. [4]); consequently, the importance of SCFAs and differential SCFA availability in human energy and substrate metabolism remains to be fully established. In patients, SCFAs have been positively correlated with body mass index (BMI) and insulinaemia, among other risk factors of the metabolic syndrome [4,14,15]. In hyperinsulinaemic subjects, rectal administration of acetate increased plasma PYY levels [16]. In the study of van der Beek et al. [6], distal colonic infusion of acetate increased fasting fat oxidation, fasting PYY levels and postprandial glucose and insulin levels. In accordance with this last finding, Perry et al. [13] reported that systemic acetate increases glucose-stimulated insulin release in mice. Conversely, Tang et al. [17] documented that acetate directly inhibits insulin secretion in mouse pancreatic islets, reinforcing again the current ‘acetate controversy’. Differences in doses, timing and patterns of exposure are plausible explanation for the discrepancies, with a continuous administration of acetate eliciting a response different than the one obtained after acute exposure or under cyclic production. To follow-up on the study by van der Beek et al. [6], it will therefore be interesting to determine whether increased postprandial glucose and insulin levels are maintained upon chronic exposure, and if and how these changes affect the host’s metabolism.

PROXIMAL VERSUS DISTAL DELIVERY

van der Beek et al. [6] decided to administer acetate via colonic infusion. Although easier, administration by oral ingestion is irrelevant when it comes to evaluating the potential benefits that could be conferred by microbiota-derived acetate. Indeed, when administered per os, acetate is absorbed in the upper part of the gastrointestinal tract with little chance to interact with the colonic mucosa. On the other hand, administration of fermentable fibres will be associated with the production of other SCFAs such as propionate with likely confounding effects.

Thus, using direct local application, van der Beek et al. [6] showed that distal, but not proximal, colonic acetate infusion led to changes in metabolic markers, namely an increase in fasting fat oxidation, fasting PYY levels, postprandial glucose and insulin levels, as well as a trend towards increased fasting acetate levels (Figure 1). As pointed out by van der Beek et al. [6], several factors could explain the influence of the site of infusion. The proximal and distal colons differ in their microbial composition, GPR43 expression profile and drainage system, as the distal colon is drained through the general circulation and, unlike the proximal part, escapes the hepatic first-pass [6]. In a first scenario, acetate could induce metabolic benefits through direct activation of signalling pathways, such as GPR43-dependent pathways, locally. Indeed, activation of colonic GPR43 can trigger the release of PYY in rodents [18]. Relevant to explain a difference between sites of infusion, GPR43 is expressed at a higher level in the distal than in the proximal colon [19]. As an alternative, but not mutually exclusively, scenario, acetate might mediate its effects through the activation of metabolic processes and molecular pathways in peripheral organs (reviewed in [4]). In this case, blood acetate concentrations would matter. In support of this hypothesis, van der Beek et al. [6] reported a trend towards increased acetate levels in systemic blood for the distal infusion only. Finally, as microbiota patterns are different in the proximal and distal parts of the colon, a different fate for the infused acetate cannot be excluded. Indeed, acetate could be transformed into butyrate through the butyryl-CoA CoA-transferase pathway whose enzymes are not ubiquitously distributed among gut microbes [20]. However, the lack of impact of distal and proximal colonic acetate infusion on plasma propionate and butyrate, whether in fasting or postprandial states, are not in favour of this last scenario.

Nonetheless, it remains to be determined whether the metabolic effects of the distal acetate infusion rely on increased systemic levels of acetate, on the activation of specific signalling pathways in the distal colon or on other mechanisms.

TOWARDS A NUTRITIONAL MODULATION OF SCFA PRODUCTION IN THE DISTAL COLON

If confirmed in further studies, the site of diffusion should be taken into account when designing a nutritional tool to the benefit of overweight/obese patients. Selection of dietary fibres with or
without structural modifications could be envisaged. Indeed, the fermentation pattern of dietary fibres is closely linked to the structure of the compound [21]. The chain length and the degree of polymerization (DP) influence the amount and profile of SCFAs produced and the portion of the bowel where fermentation takes place [21–23]. For instance, inulin (DP 3–60) induced a higher production of propionate and butyrate than oligofructose (DP 2–20) [23]. Also, to promote colonic acetate production/release, an approach similar to the one used by Chambers et al. [24] might constitute a sustainable way to proceed. Chambers et al. [24] designed an inulin-propionate ester as a tool to channel the delivery of a high quantity of propionate directly in the colon. Whether a strategy of such kind would be useful to deliver a significant fraction of the acetate preferentially in the distal rather than proximal colon requires confirmation before any further clinical investigation. In such an undertaking, in vitro models such as the Simulator of the Human Intestinal Microbial Ecosystem (SHIME) represent valuable tools [23].

The study by van der Beek et al. [6] highlights a second point that must be taken into account when considering increasing colonic acetate for therapeutic purposes: the importance of the dose. The effects of acetate infusion on fasting fat oxidation and fasting PYY levels were significant only at the highest dose. The effects of acetate preferentially in the distal rather than proximal colon requires confirmation before any further clinical investigation. In spite of technological advances, assessing the production of SCFAs in vivo in response to chronic consumption of dietary fibres remains challenging. As SCFAs are in a dynamic equilibrium between production, absorption, distribution, metabolism and excretion throughout the body, faecal SCFAs might not appropriately reflect local in situ SCFA production. Strikingly, depending on the studies, consumption of dietary fibres known to promote bacterial fermentation (e.g. inulin) has been associated with increased as well as reduced faecal acetate concentrations in humans [15,25]. Snapshot measurement of SCFAs at one time point in one compartment might also not appropriately assess whole SCFA production [8]. As an alternative, Boets et al. [26] used a stable-isotope dilution method to quantify colonic production of SCFA in vivo in humans consumed dietary fibres. They estimated that ingestion of 15 g of inulin leads to a production of 137±75 mmol of acetate over 12 h. In accordance with these findings, Robertson et al. [27] showed that supplementation with resistant starch for 4 weeks (30 g/day) leads to a net increase in postprandial plasma acetate levels [27], suggesting that modulation of plasma acetate levels through nutritional intervention is achievable in humans.

CONCLUSIONS

With this pilot study, van der Beek et al. [6] reinforce the interest in acetate as a potential therapeutic tool to modulate host metabolism. In view of the pilot results reported by this group and others, long-term studies to evaluate the impact of SCFAs on metabolic health in humans are clearly warranted. The challenge ahead of us is to determine whether the metabolic benefits of acetate rely on the production (or infusion) site, increased systemic levels, activation of specific pathways in the (distal) colon or on other alternative mechanisms. Answering these questions will assist the researcher in shaping nutritional or pharmacological tools for increasing health or for therapeutic purposes in the context of obesity-associated disorders.

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DECLARATION OF INTEREST

The authors declare no conflicts of interest.

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