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Colonic bacterial metabolites and human health

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The influence of the microbial–mammalian metabolic axis is becoming increasingly important for human health. Bacterial fermentation of carbohydrates (CHOs) and proteins produces short-chain fatty acids (SCFA) and a range of other metabolites including those from aromatic amino acid (AAA) fermentation. SCFA influence host health as energy sources and via multiple signalling mechanisms. Bacterial transformation of fibre-related phytochemicals is associated with a reduced incidence of several chronic diseases. The 'gut–liver axis' is an emerging area of study. Microbial deconjugation of xenobiotics and release of aromatic moieties into the colon can have a wide range of physiological consequences. In addition, the role of the gut microbiota in choline deficiency in non-alcoholic fatty liver disease (NAFLD) and insulin resistance is receiving increased attention.

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Introduction

The human large intestine is colonised by dense microbial communities that utilise both diet-derived and host-derived energy sources for growth, predominantly through fermentative metabolism. This highly diverse community has the capacity to perform an extraordinary range of biochemical transformations that go well beyond those encoded by the host genome, and these activities exert an important influence upon many aspects of human health. Metabolites formed by the gut microbiota are largely determined by the composition of the diet and the pattern of food intake, and it is now clear that the species composition of the colonic microbiota is itself altered by the diet [1•,2,3••]. This review will consider selected examples where recent progress has been made in understanding the links between diet, gut microbial activity and metabolites relevant to health.

Bacterial metabolites derived from the fermentation of plant-derived carbohydrates and their impact on the host

Many carbohydrates (CHOs) present in plant-derived foods are digested slowly, if at all, in the small intestine, making them available for microbial fermentation in the large intestine. Intake of starch that is resistant to digestion in the small intestine (resistant starch) can have benefits for metabolic health [4] and results in changes in the gut microbiota [1•]. Recent work also shows a beneficial influence of whole grain intake upon inflammation, again with concomitant changes in the gut microbiota [5•]. Diet-induced changes in the metabolic activity of the gut microbiota are thought likely to mediate these effects.

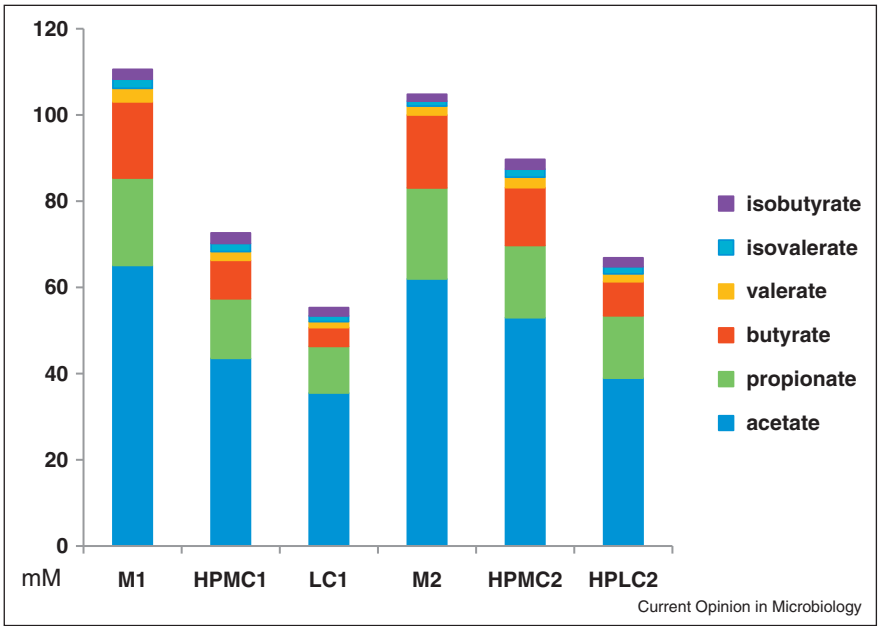
Hexose and pentose sugars are fermented by isolated human colonic bacteria via pathways leading to the formation of acetate, succinate, propionate, butyrate, formate (short chain fatty acids (SCFA)), lactate, ethanol, hydrogen and CO_2, depending on the strain and species. Butyrate formation occurs in certain Firmicutes bacteria, either via butyrate kinase (in many *Clostridium* and *Coprococcus* species) or via butyryl CoA:acetate CoA transferase [6]. The latter pathway is found in the numerically predominant butyrate-producing species of *Roseburia*, *Eubacterium rectale*, *Eubacterium hallii* and *Faecalibacterium prausnitzii*, and involves the net uptake of external acetate [7]. Acetate is produced by most anaerobes, including acetogens that are able to perform reductive acetogenesis from formate or hydrogen plus CO_2. Producers of succinate and propionate largely belong to the phylum Bacteroidetes, but also include some Firmicutes. Lactate can be formed by many groups, but is generally converted into acetate, propionate or butyrate by a subset of lactate-utilizing species [8]. Formation of the gases hydrogen and CO_2 varies widely between species in pure culture; in the mixed community these products are partially converted to acetate, methane or hydrogen sulfide [9]. The net outcome of all of these complex cross-feeding interactions for a typical healthy microbiota is that, in faecal samples, acetate is the dominant SCFA detected (typically 40–70 mM) followed by propionate and butyrate (each 10–30 mM) [10]. While alternative products such as ethanol,

succinate and lactate are normally found at lower concentrations, they can accumulate in some circumstances and a link has been proposed between endogenous ethanol formation and non-alcoholic steatohepatitis (NASH) [11].

At these concentrations, SCFA have a major impact on the large intestinal environment and on absorption from the lumen. While butyrate is largely utilised by the gut epithelium, and propionate is largely metabolised in the liver, acetate is the SCFA that reaches the highest concentrations in plasma [10]. There is increasing evidence that acetate plays an important role in controlling inflammation and in combating pathogen invasion [12,13]. Acetate and lactate were also found recently to influence cyclin gene expression and epithelial cell proliferation in a pH-dependent manner *in vitro* [14]. The importance of butyrate as an energy source for epithelial cells has long been recognised, but its role in regulating inflammation, cellular differentiation and apoptosis, and in helping to prevent colorectal cancer, is still emerging [15]. Interestingly, butyrate was recently found to be the most potent SCFA in activating the AP-1 signalling pathway in epithelial cell lines [16]. Interactions have been recognised between SCFA and the host cell receptors FFAR2 and FFAR3 that might influence satiety, protect against diet-induced obesity and improve insulin sensitivity, with propionate considered to have a potentially important role [17,18]. In view of this it is important to understand how diet and microbiota composition can influence relative, as well as total, SCFA production. Studies in obese subjects on weight loss (WL) diets demonstrate that dietary intake of CHO has a major impact on faecal SCFA concentrations [19,20••] presumably reflecting decreased fermentation in the colon (Figure 1). More surprising, however, is that butyrate responded disproportionately as a percentage of total SCFA, an effect that correlates with a marked decrease in the *Roseburia-E. rectale* group of butyrate-producing bacteria [19]. This may be explained by the greater dependence of this group, compared with other members of the microbiota, on intake of resistant dietary CHOs, and provides evidence that SCFA relative production rates are responsive to diet composition. An inverse relationship has been noted between faecal pH and butyrate concentration *in vivo* [21]; this is likely to reflect the great competitive ability of some butyrate-producers at the reduced pH arising from active fermentation in the proximal colon [22].

Decreased numbers of butyrate-producing bacteria, especially *F. prausnitzii*, have been noted in patients suffering from Crohn's disease. This species exerts anti-inflammatory effects that appear to involve soluble factors in addition to butyrate [23]. Interestingly, *F. prausnitzii* was recently shown to diminish the impact

Figure 1



Impact of reduced CHO weight loss (WL) diets in male obese volunteers on faecal SCFA concentrations. Data are from two separate dietary cross-over studies that are reported in [19] (study 1) and [20••] (study 2): M – weight maintenance diet (360–400 g day^{-1} CHO, 22–28 non-starch polysaccharide 'fibre' (NSP)), HPMC – high protein, moderate CHO WL diet (164–182 g day^{-1} CHO, 12–13 NSP), HPLC – high protein, low CHO WL diet (23–24 g day^{-1} CHO, 6–9 NSP). In addition to the evident decrease in total SCFA, both studies detected a significant decrease in percent butyrate among SCFA, while in study 2 the percent of minor SCFA (valerate, isobutyrate, isovalerate) that were derived from amino acid fermentation increased, reflecting the higher protein intake on the WL diets.