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## Conference on 'Carbohydrates in health: friends or foes'
## Symposium 3: Non-digestible carbohydrates, gut microbiota and obesity

# The multifactorial interplay of diet, the microbiome and appetite control: current knowledge and future challenges

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The recent availability of high-throughput nucleic acid sequencing technologies has rapidly advanced approaches to analysing the role of the gut microbiome in governance of human health, including gut health, and also metabolic, cardiovascular and mental health, *inter alia*. Recent scientific studies suggest that energy intake (EI) perturbations at the population level cannot account for the current obesity epidemic, and significant work is investigating the potential role of the microbiome, and in particular its metabolic products, notably SCFA, predominantly acetate, propionate and butyrate, the last of which is an energy source for the epithelium of the large intestine. The energy yield from dietary residues may be a significant factor influencing energy balance. This review posits that the contribution towards EI is governed by EI diet composition (not just fibre), the composition of the microbiome and by the levels of physical activity. Furthermore, we hypothesise that these factors do not exist in a steady state, but rather are dynamic, with both short- and medium-term effects on appetite regulation. We suggest that the existing modelling strategies for bacterial dynamics, specifically for growth in chemostat culture, are of utility in understanding the dynamic interplay of diet, activity and microbiomic organisation. Such approaches may be informative in optimising the application of dietary and microbial therapy to promote health.

**Fibre: Microbiome: Appetite: Obesity: SCFA**

## Overview

The availability of high-throughput nucleic acid sequencing technologies has facilitated a range of new approaches to analysing the role of the gut microbiome in governance of human health[1]. Modern techniques suggest a role for the microbiome maintenance of, not only gut health but also systemic conditions, including cardiovascular health[2], mental health[3] and obesity[3]. Despite wide media focus on excess energy intake (EI), recent scientific studies suggest EI perturbations at the population level cannot account for the current obesity epidemic[4]. The microbiome is responsible for the production of a highly complex and highly dynamic metaexometabolome. Well-known components of this include the SCFA acetate, propionate and butyrate, the last of which is an energy source for the epithelium of the large intestine[5], as well as an inhibitor of histone deacetylation (and thereby cell fate determination)[6]. The energy yield from dietary residues entering the large intestine may account for as much as 10 % of EI[7] and is therefore a significant factor influencing energy balance. The guiding theme of this review is that this contribution towards EI is governed by EI, diet composition, the composition of the microbiome and levels of physical activity. Furthermore, we hypothesise that these factors do not exist in a steady state, but rather are dynamic, with both short- and medium-term effects

**Abbreviations:** EI, energy intake; FFAR, free fatty acid receptors; GI, gastrointestinal; IGN, intestinal gluconeogenesis.
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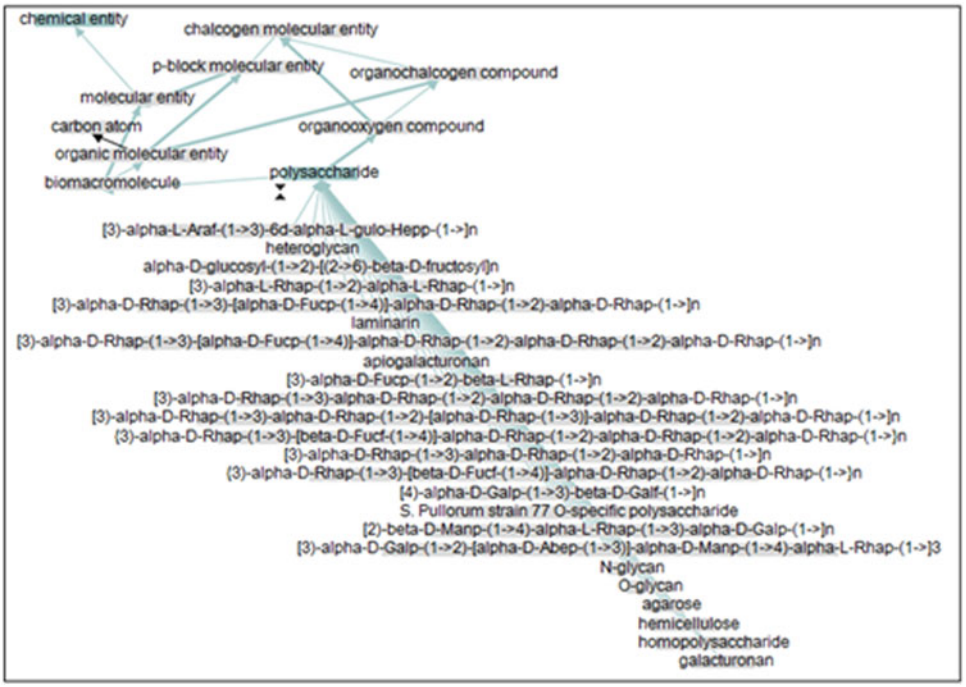


**Fig. 1.** (colour online) A chemical ontology for fibre. Accessed from ChEBI (www.chebi.ebi.ac.uk), 8 July 2014.

on appetite regulation. There is therefore potential to modulate this component of EI through a range of modalities to promote health.

## Fibre/dietary residue

### *Scope of definitions of dietary fibre*

Fibre is a component of diet which is highly complex and inconsistently defined. Approaches to the definition vary from the biochemical, to the physiological, to the functional. The Englyst definition, for example, is 'non-starch polysaccharides'[8]. This is in line with other definitions within nutrition, although it is notable for the element of exclusion which places fibres in the general class of polysaccharides outwith the subclass of starches. Fig. 1 provides top-level indication of the potential chemical complexity of this ontology (accessed from ChEBI). However, each endpoint within this ontology masks further factors, including the degree of polymerisation: the nature and extent of polymerisation of side-chains on any polysaccharide backbone. Against this rigid definition is the Association of Official Agricultural Chemists-adopted version by Prosky[9], that fibres are 'remnants of plant cells resistant to digestion by human digestive enzymes'. This definition introduces a physiological component, insofar as resistance to digestion implicates human physiology, but its relevance to non-human subjects and human subjects with abnormal digestive capacity is questionable. For example, is fibre different for animals with different profiles of digestive enzymes? Furthermore, what is the relationship between fibre and personalised medicine? For example, in the case of an inborn error of metabolism which may impair intraluminal digestion or absorption: is this definition personal, with each of us potentially having a different profile of fibres? Finally, it introduces a source component, in this case botanical, which raises the question of how fungi fit within this classification. The definition was further extended to include an aspect of functionality in the following Scientific Advisory Committee on Nutrition (SACN) statement:

> *SACN consider that a material can be considered as dietary fibre if it is resistant to digestion and absorption in the small intestine and has a demonstrable physiological effect potentially associated with health benefits in the body, such as increasing stool bulk, decreasing intestinal transit time or decreasing post prandial glycaemia. Evidence only of increased fermentation in the gut should not be included under this definition, since although this has a direct effect on the microflora, it must also be shown to have a demonstrable benefit to the host to be considered as dietary fibre.*
>
> SACN Statement August 2008

This extension to the Prosky definition includes and exemplifies health benefits of fibre, yet such advantages are notoriously difficult to demonstrate and attribute. Additionally, it recognises that functionalities may occur beyond the gut, implying indirect mechanisms, although other classes of compound potentially yielding the same intermediate effectors would be excluded from this definition. The SACN statement does not reflect the source (botanical or otherwise) of fibre, but does introduce difficulties of defining fibres in potentially personalised terms.

This extended cynicism about mainstream definitions could be coupled to a simple, unifying observation: bacteria cannot read research papers or position statements. The extent of compounds which reach the colon has

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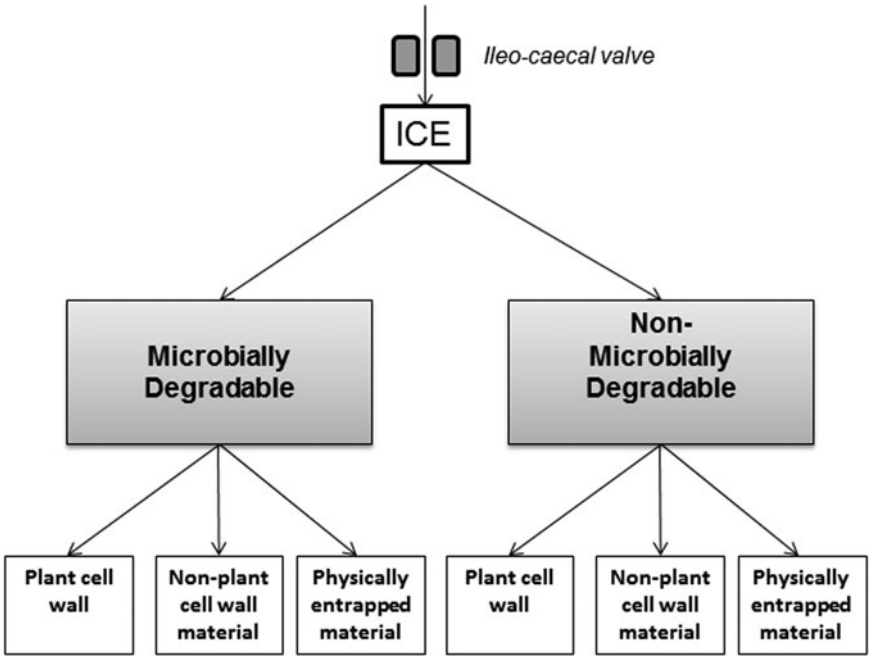


**Fig. 2.** An alternative definition of fibre. Based on Ha *et al.*[11] this definition encompasses all material able to enter the colon (ileocaecal effluent; ICE), as available for microbial metabolism. Some components are readily metabolised, some highly resistant to metabolism.

been demonstrated, *inter alia*, in studies of differentially diced almond skins, which were found to yield a range of macro- and micro-nutrients[10]. It can therefore be argued that the colon environment is not solely nourished by fibres, but by the totality of the ileocaecal effluate: the material that passes through the ileocaecal valve, whether intact or part-digested, whether of plant, animal or fungal origin, whether polysaccharide or not. For the purposes of a review of interactions between fibres and the microbiome, this definition facilitates the full scope of potential interaction between dietary factors and the microbiome in understanding the production of the exometabolome. Our concept of ileocaecal effluent resembles the definition of fibre proposed by Ha 'Any dietary component that reaches the colon without being absorbed in a healthy human gut'[11]. The authors critically assimilate the overarching effects of fibre, reproduced in Fig. 2; the division between fermentable and non-fermentable fibres. Fermentable fibres are generally progressively degraded to metabolic endproducts including SCFA.

### *The nature of the exometabolome*

Major products ensuing from this fermentation are the SCFA acetate, butyrate and propionate, which can be utilised for lipid or gluconeogenesis[12]. SCFA have been estimated to provide 10 % of the total dietary energy in human subjects, and host epithelial cells derive 60–70 % of their energy supply from SCFA, particularly butyrate[13]. Acetate and propionate are transported across the mucosa and into the hepatic portal and may be detected in the systemic circulation[14] although circulating concentrations of butyrate are disproportionately depleted in the circulation due to mucosal metabolism. Other key exometabolites include glucose, vitamins and precursors to neuropeptides. The gastrointestinal (GI) tract has a panel of cell types sensing and responding to these molecules; this interaction is linked to the nervous system, and thereby the gut–brain axis[15].

## Microbiome

The human GI tract houses a very complex microbial ecosystem of more than 100 trillion micro-organisms, ten times greater than the total number of the human cells in the body. Human-associated bacteria are dominated by two phyla; Firmicutes and Bacteroidetes, with Proteobacteria, Actinobacteria and Verrucomicrobia present in minor proportions[16,17], and each phyla containing many different bacterial species[18].The gut microbiota plays an important role in metabolism, immune function, protection of the host from pathogens and bidirectional communication between the GI tract and the central nervous system[19]. Dysbiosis, an aberrant state of imbalance of the gut microbiota, has been associated with a diversity of diseases and syndromes such as inflammatory bowel disease, irritable bowel syndrome, colorectal cancer, atopy, anxiety, depression, type II diabetes and metabolic syndrome. The role of the gut microbiota in obesity has been of particular interest, especially given that the global prevalence of obesity in both children and adults is rapidly increasing[20], and is a leading cause of preventable disability and death. Obesity results from a sustained net positive energy balance whereby EI exceeds energy output. In addition, host differences in the

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ability to store and expend energy contribute to obesity[21]. A new but growing body of evidence suggests the gut microbiota, through its role as an interface between nutrients and the host, may assist body weight regulation. The gut microbiota can affect nutrient acquisition and energy harvest, as well as producing exometabolites that in turn may regulate host metabolic pathways[6,22].

Early indications that the gut microbiota was involved in obesity came when metabolically obese mice, with a mutation in the leptin gene, were shown to have a significantly different microbiota compared with mice without the mutation[23]. Further investigation indicated that the ratio of Firmicutes to Bacteroidetes in the gut microbiota of obese mice was shifted in favour of Firmicutes, while lean mice were dominated by Bacteroidetes[24]. In human subjects, the gut microbiota composition can respond to changes in body weight and is altered in obese compared with non-obese individuals[18]. Bacteroidetes may be responsive to EI because their levels increase when body weight is reduced following a reduced energy diet[25], although numerous human studies have failed to demonstrate a consistent relationship between obesity and the ratio of Firmicutes to Bacteroidetes at both the phylum- and species-levels[26].

Hydrogen-producing Prevotellaceae and hydrogen-utilising methanogenic Archaea were more abundant in obese individuals suggesting a higher energy harvest in the large intestine to hydrogen transfer between bacterial and archaeal species[27]. Changes in the composition of the gut microbiota have been linked with (i) suppression of intestinal fasting-induced adipocyte factor, which is a contributing factor to enhanced fat deposition[28]; (ii) increased capacity to harvest energy from food; (iii) low-grade inflammation due to activation of toll-like receptors, endotoxin and proinflammatory cytokine production[29,30]. Approximately 5 % of the ingested energy is lost in the stool and urine[31]. Altered nutrient load over a 3-d period induced changes in the gut microbiota in both obese and non-obese individuals, despite statistically significant differences in the composition of the lean and obese microbiome at baseline under a weight maintaining diet[32]. In the case of lean subjects, a 20 % increase in Firmicutes (and a corresponding decrease in Bacteroidetes) was observed over the 3-d period and was associated with 627·60 kJ (150 kcal) increase in energy absorption.

SCFA have been implicated in metabolic diseases, including obesity[33]. Higher levels of faecal SCFA, mainly butyrate and propionate, have been reported in obese adults[34] and children[35], compared with lean individuals. Changes in the concentration and proportion of individual SCFA may be in line with changes in the bacterial groups present[12,35].

## Appetite control

There are two general definitions of appetite[36]. The first relates to food preference, selection and intake and the motivation to eat, while the second refers to qualitative and sensory aspects of food, including the impact of environmental stimulation. These eclipse homeostatic theories which suggested that feeding corresponds to energy/nutrient deficit or excess[37], yet it is likely that a suite of homeostatic and complex non-homeostatic factors determine the overall expression of appetite. Appetite is normally described in terms of hunger, satiation and satiety. Hunger is associated with emptiness of the stomach, irritability and light-headedness[36]. Human subjects can and do, however, display hunger for other reasons: the smell, sight or even thought of food can initiate feeding[38]. Eating triggers a cascade of metabolic signals that can suppress hunger and inhibit further consumption[39]. Satiation is the point of satisfaction that results in meal termination[38,40,41]. Satiety is the (modifiable) post-ingestion period of repletion which influences the time of the next eating occasion[42].

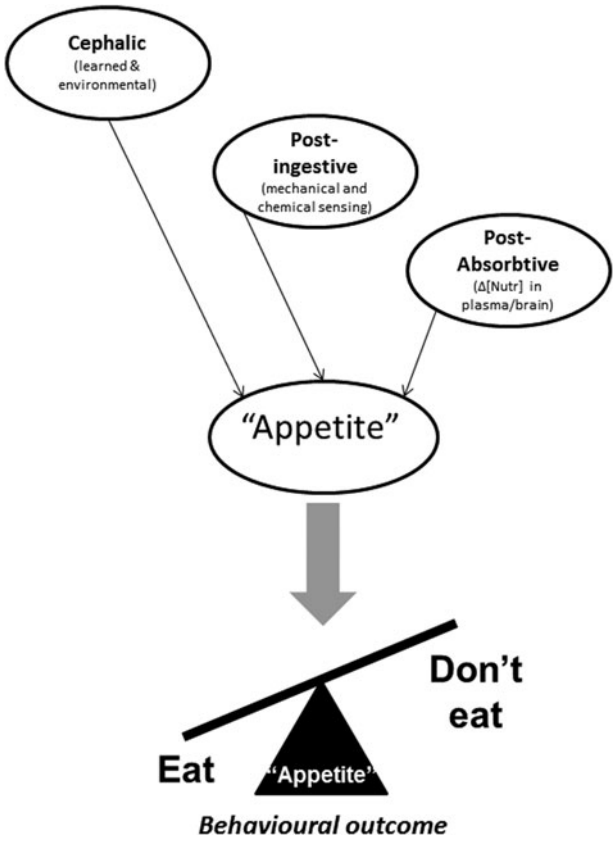


**Fig. 3.** Tires of appetite regulation by SCFA.

Appetite is controlled by multiple integrated physiological signals (see Fig. 3). Short-term signals help regulate meal initiation and termination, whereas long-term, humoral signals play a central role in body weight regulation[43]. This conceptual framework for examining the impact of feeding is continually updated to represent an increasing number of factors encompassing peripheral physiological and metabolic events, and brain responses that play important roles in appetite control[44]. The GI tract responds to feeding in three integrated phases: cephalic, post-ingestive and post-absorptive, all of which depend on parasympathetic nerve transmission. The cephalic phase occurs at the point of food selection

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**Table 1.** The secretory products of enteroendocrine cells of the colon and rectum and their actions

| Peptide | Actions |
|---|---|
| 5-HT | Intestinal motility; intestinal secretion; visceral sensation; appetite reduction |
| Glicentin | Stimulates mucosal enterocyte proliferation; inhibits gastric emptying |
| GLP-1 | Incretin effect; delays gastric emptying; postprandial satiety, inhibits energy intake |
| GLP-2 | Stimulates mucosal enterocyte proliferation, enhances digestive and absorptive capacities of intestine, inhibits gastric secretion |
| Oxyntomodulin | Inhibits gastric emptying, reduces gastric motility, inhibits food intake |
| PYY | Inhibits gastric emptying and intestinal motility; inhibits gastric acid secretion and pancreatic exocrine function; suppresses appetite; stimulates mucosal enterocyte proliferation |
| Somatostatin | Major inhibitory hormone for digestive endocrine and exocrine function; stimulates colonic peristalsis; potential for reducing food intake |

5-HT, serotonin; PYY, peptide YY; GLP-1, glucagon-like peptide 1; GLP-2, glucagon-like peptide 2.
Table taken from Gunawardene Corfe & Staton[57] with additional information from[81–83].

and early ingestion, and is thus stimulated by conditioned processes and organoleptic factors[45,46]. It is held that post-ingestive satiation signals arise largely from mechanical distension, whereas signals from the GI tract derive predominantly from the chemical effects of food[47]. In contrast, post-absorptive effects are the result of interplay between hormones and the hypothalamic region of the brain that respond to fluctuating concentrations of nutrients in the portal vein, plasma and brain.

### *Impact of the exometabolome on post-ingestive appetite regulation*

Landmark human studies have shown intestinal nutrient infusions can reduce food intake with rapid effects[48–50], indicating that satiation signals must originate from the gut as well as post-absorptively. Numerous hormones, neurotransmitters and peptides stimulate orexigenic or anorexigenic responses. Many peptide hormones are produced in the GI tract and released in response to nutritional stimuli. Anorexigenic hormones include cholecystokinin, glucagon-like peptide-1 and -2, glucose-dependent insulinotropic polypeptide, oxyntomodulin, pancreatic polypeptide, peptide histidine isoleucine, peptide histidine valine, peptide YY and somatostatin)[51,52]. Enteroendocrine cells (EEC) represent <1 % of the mucosal cell population, yet form the largest endocrine system in man[53], and is populated by singly distributed EEC which release a very significant portion of appetite regulating hormones[54] (Table 1). EEC have a characteristic flask-shaped morphology and have been divided into at least sixteen cellular subtypes based on the major products they produce and secrete[55], although this model is contested and a continuum of cell types has also been proposed[56].

The primary EEC types in the colon are D cells, L cells and EnteroChromaffin cells[57]. While all cell types may be found along the colon, EnteroChromaffin are the most abundant, and D cells the least, with a progressive increase in the proportion of L cells along the caecorectal axis. As summarised in the present review, these cells harbour peptide/hormones involved in appetitive regulation, including peptide YY, glucagon-like peptide 1, glucagon-like peptide 2 and oxyntomodulin. Intriguingly the EnteroChromaffin subclass also contain serotonin and reports suggest that as much as 95 % of the body's serotonin may exist in the gut[58]. Serotonin has been implicated in appetitive regulation, mood control and regulation of gut transit. This underwrites plausible links between luminal content, motivation to eat and wider aspects of regulation of colorectal content through modulation of transit time. These factors are explored in greater detail later.

SCFA are important signalling components within the gut–brain axis, the system of communication between the gut and the brain[19,59] which interacts directly with gut endocrine cells, and stimulates secretion of peptide YY by activating two G-protein-coupled receptors. Enteroendocrine carry free fatty acid receptors (FFAR) on their surface which have differential affinity for SCFA and which signal the release of appetitive hormones from EEC[60]. As components of the exometabolome, SCFA therefore act as key molecules governing the sensing–signalling pathway linking luminal metabolism to appetite regulation.

Our group have recently identified a further plausible mechanism of action. A significant body of literature suggests that butyrate is a potent regulator of numbers of proliferating cells in the colon crypt. We recently demonstrated an inverse association between SCFA and the numbers of EEC cells in the crypt[61]. Mathematical modelling suggests that SCFA may modulate differentiation pathways on exit from the stem cell compartment[62]. Taken together these data suggest two possible tires of regulation of post-ingestive appetite by the exometabolome: (1) an acute response in terms of regulating release of anorectic hormones; (2) an adaptive modulation of numbers of EEC and thereby available pools of appetite-regulatory hormones.

### *Impact of the exometabolome on post-absorptive appetite regulation*

Post-absorptive signals are stimulated by the entry of nutrients into the portal vein of the liver, or by fluctuating nutrient concentrations in the plasma and brain[63]. These signals act (via the hypothalamic region of the brain and vagus nerve) on the periphery and central nervous system and also interact with long-acting adiposity hormones (such as leptin) that help regulate body weight *ibid*. Two key areas are impacted by the exometabolome: via intestinal gluconeogenesis (IGN) and through pansystemic propionate sensing.

Gluconeogenesis has until relatively recently been viewed as a primarily hepatic and renal phenomenon, and is not positively associated with health, reflecting excess energy

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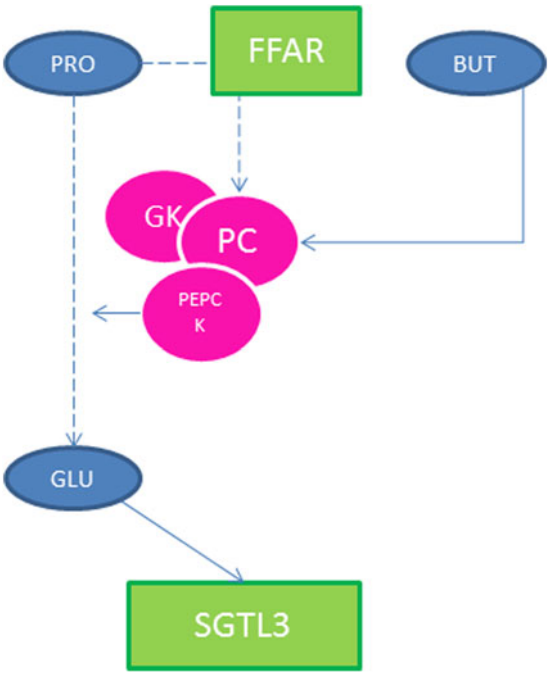


**Fig. 4.** (colour online) Intestinal gluconeogenesis pathway. PRO, propionate; FFAR, free fatty acid receptor; BUT, butyrate; GK, glucose kinase; PC, phosphoenolpyruvate carboxykinase; PEPC K, phosphenolpyruvate carboxykinase; GLU, glucose; SGTL3, sodium-coupled glucose co-transporter.

intake. Relatively recently the intestine has been identified as a site of gluconeogenesis (distinguished as IGN)[64]. IGN is regulated by both butyrate and propionate. Butyrate acts to govern the levels of IGN enzymes in the mucosa. In contrast, propionate is both a substrate for IGN and is a regulator of IGN enzyme activity mediated via FFAR3 signalling (Fig. 4)[65]. The present paper therefore also suggests emergent distinctions between the fates and activities of SCFA. Intestinally produced glucose is transported to the hepatic portal vein where it is directly sensed by sodium-coupled glucose co-transporter[66]. Critically, in contrast to hepatic and renal gluconeogenesis, IGN is associated with positive health outcomes[65].

Post-ingestive appetite regulation may also occur at the level of FFAR3 signalling. There is growing recognition that FFAR family receptors, including FFAR3 are expressed on a wide range of tissues, including adipose and liver. The role of FFAR3 in non-gut tissue is reviewed elsewhere[67].

### *Impact of the exometabolome on cephalic phase of appetite regulation*

The impact of exometabolites upon cephalic phase of appetite has not been well explored; however, it is reasonable to hypothesise that it does contribute to the wider mechanisms of appetite control as precedents have been shown in microbiome–mood interactions. For example, perturbations of the gut flora have been associated with schizophrenia and depression[68,69]; probiotic interventions in mouse models have demonstrated anxiolytic potential of microbial intervention[70]; probiotic interventions have also shown impact upon brain activity[71] and on cognitive outcome[72]. Recent reviews have suggested potential mechanisms of action, including modulation of afferent signalling by SCFA, cytokine-mediated responses triggered through Toll-like receptors in the mucosa responding to the microbiome, and modulation of γ-aminobutyric acid mediated signalling[15]. As a strong evidence-base is emerging for a role of the microbiome and exometabolome in governance of mood and cognition, it seems likely that this will in time extend through to cephalic phase appetite control.

## Modification of the microbiome by alteration of transit (the chemostat analogy)

Although obesity and obesity-related disorders have been linked with alterations in the gut microbiota, less attention has been directed towards investigating lifestyle aspects of obesity, such as exercise and diet, and their effect on the microbial and physical environment of the GI tract[73]. In a recent study, elite athletes had a significantly more diverse gut microbiota compared with non-athletic size matched (high BMI about 30) and age/sex-matched (BMI < 25) control groups[74]. As the elite athlete group also consumed a significantly different diet, which provided more energy daily from carbohydrates, proteins and fat compared with the control groups, the present study suggested that both diet and exercise were driving factors in changing gut microbial diversity. Exercise has also been shown to decrease transit time, particularly through the descending colon[74,75]. Previous reports have suggested however, that physical activity does not necessarily improve overall GI transit[76].

It may be convenient therefore to view the colon as a chemostat, a commonly used form of bioreactor, which has been applied in microbiological settings for the determination of growth parameters (Fig. 5). In this simple model the ecosystem is fed at a specific rate (the dilution rate) which is also reflected in the rate of effluent production. The population within this system will have a growth rate (μ) proportional to the dilution rate (*D*). At a certain dilution rate $\mu_{max}$ is reached: the maximal growth rate for a particular species (in the context of an ecosystem this will be for a specific species as each will have a unique $\mu_{max}$); at this point the species will start to dilute from the system. The dilution rate therefore represents an extremely strong selective pressure upon the microbiome. As discussed in the previous sections, fibre intake as well as physical activity levels will influence transit time, which is analogous to the dilution rate in a chemostat. Data suggest that individuals on high-fibre diets lose more energy in faecal material than those on lower-fibre diets with an equivalent energy content[77], supporting a model whereby reduced energy harvest associates with a factor affecting transit.

We therefore argue that a contributing longitudinal effect of high-fibre intakes, or high physical activity, or the combination thereof is the modification of the microbiome by exerting a specific selective pressure. Contrastingly, excessive slow values for dilution rate, *D*, will provide

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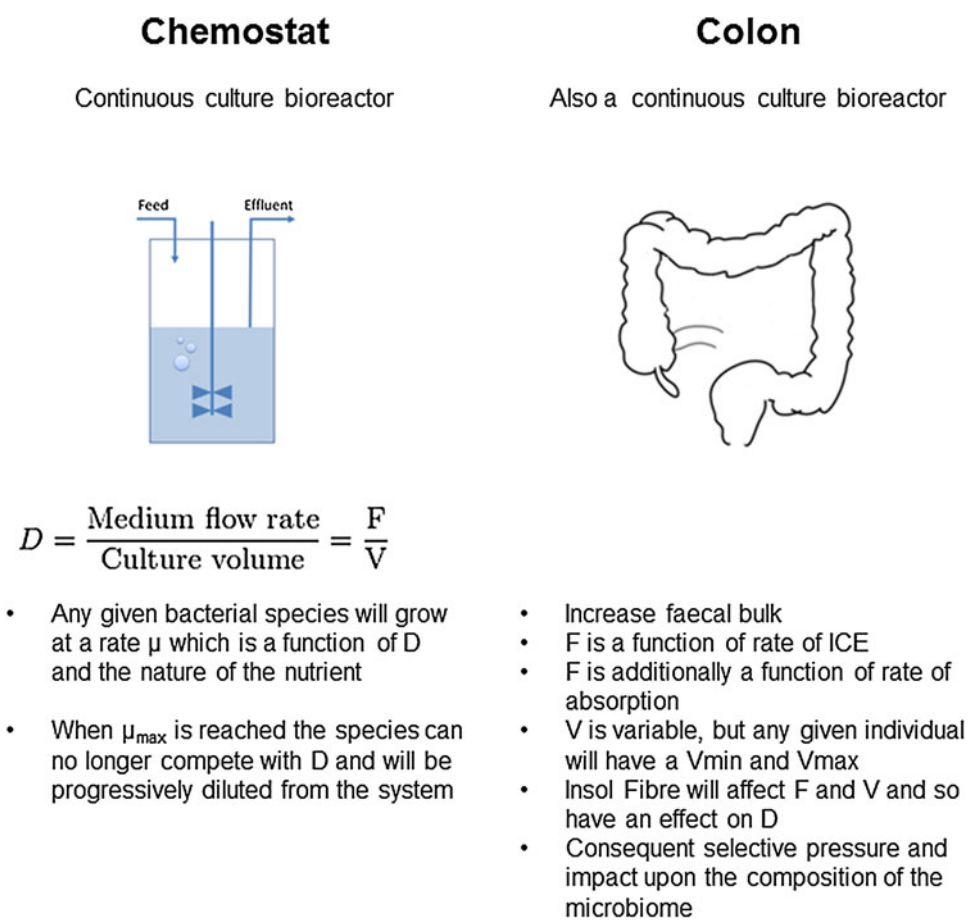


**Fig. 5.** (colour online) Analogy between the chemostat and the colon. ICE, ileocaecal effluent. Chemostat image: chemistry.about.com, colon image: www.clker.com

opportunities for these microbial products to interact with the host epithelium, potentially increasing host energy harvest in the case of SCFA, and elevating exposure to pro-inflammatory signalling and cytotoxic molecules.

## Summary and future directions

The question of whether alterations in gut microbiota are a cause or a consequence of obesity still remains unclear, although evidence from observational and intervention studies in human subjects appears to suggest that both the microbiota and diet play a significant role in body weight regulation, beginning at birth. Although the utility of animal models for conducting more controlled experiments investigating the differences between the obese and lean microbiota has been established, translation to research in human subjects has proved less fruitful in providing a clear consensus concerning the role played by the balance between the most abundant bacterial phyla in the human gut. Indeed, the emerging evidence indicates that even the effect of individual bacterial species cannot be disregarded from study. This means that moving towards the use of high-resolution, standardised analytical techniques for surveying the gut microbiota, combined with well-designed human studies taking all of the confounding variables (e.g. age, sex, ethnicity, diet and genetic factors) into account, may allow us to identify a specific consortium of microbes that contribute to obesity, elucidate their modes of action via host and diet interactions, and evaluate novel strategies to regulate energy balance in obese individuals. Such strategies may for example include approaches to modify (or restore 'normality' to the microbiota in order to restore energy balance. Changes in gut microbiota composition have been observed after consumption of an energy-restricted diet in overweight and obese subjects[26]. Inconclusive evidence exists on the effect of supplementation with lactobacilli and bifidobacteria, alone or in combination with prebiotics, on weight management in human subjects[78–80]. As such, intervention strategies are an attractive approach to appetite management through restoration of ecological balance in the gut.

## Key conclusions and areas for future research

Main things to consider are: (1) Fibres are inconsistently defined and an oversight of the totality of nutrients entering the large bowel may be more informative.

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(2) Perturbations in the microbiome associate with obesity and increased energy harvest. The relationship between the diet and microbiome and host health is mediated considerably by the exometabolome. (3) Most studies to date are associative and greater emphasis needs to be placed on longitudinal or prospective trials. (4) The relationship between the exometabolome and the host is dynamic and multifactorial; reductionist approaches are unlikely to yield an insight into health benefits.


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None.


## Conflicts of Interest

None.

## Authorship

B. M. C. conceived the scope of the review, reviewed fibre biochemistry and produced integrative hypotheses; C. J. H. reviewed appetitive aspects, M. J. B. and I. G. reviewed microbiological aspects, BMC merged text. All authors reviewed and approved the manuscript prior to submission.

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