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"Fibre, Gut Microbiome and Appetite"

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

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Abstract

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, but also metabolic, cardiovascular, and mental health, *inter alia*. Recent scientific studies suggest EI perturbations at 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 short-chain fatty acids, 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 toward EI is governed by energy intake, diet composition (not just fibre), by the composition of the microbiome, and by levels of physical activity. Furthermore we hypothesize 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 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 oraganisation. Such approaches may be informative in optimising the application of dietary and microbial therapy to promote health.

1. 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, 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 population level cannot account for the current obesity epidemic (4). The microbiome is responsible for production of a highly complex and highly dynamic metaexometabolome. Well known components of this include the short-chain fatty acids 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 toward EI is governed by energy intake, diet composition, the composition of the microbiome, and levels of physical activity. Furthermore we hypothesize that these factors do not exist in a steady state, but rather are dynamic, with both short- and medium-term effects on appetite regulation. There is therefore potential to modulate this component of EI through a range of modalities to promote health.

2. Fibre /Dietary Residue

2.1 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 08.07.15). 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 (AOAC)-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-humans and humans 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.*

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 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 ileo-caecal effluate (ICE) - 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 ICE 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 Figure 2 – the division between fermentable and non-fermentable fibres. Fermentable fibres are generally progressively degraded to metabolic endproducts including short-chain fatty acids

2,2 The nature of the exometabolome

Major products ensuing from this fermentation are the short chain fatty acids (SCFAs) acetate, butyrate and propionate, which can be utilised for lipid or gluconeogenesis (12). SCFAs have been estimated to provide 10% of total dietary energy in humans, 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 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).

3. Microbiome

The human GI tract houses a very complex microbial ecosystem of more than 100 trillion microorganisms, 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 energetic balance whereby energy intake exceeds energy output. In addition, host differences in the 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 to 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, whilst lean mice were dominated by Bacteroidetes (24). In humans, the gut microbiota composition can respond to changes in body weight and is altered in obese compared to non-obese individuals (18). Bacteroidetes may be responsive to calorie intake because their levels increase when body weight is reduced following a reduced calorie 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-level (26).

Hydrogen-producing Prevotellaceae and hydrogen-utilizing methanogenic Archaea were more abundant in obese individuals suggesting a higher energy harvest in 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 (Fiaf), which is a contributing factor to enhanced fat deposition (28), (ii) increased capacity to harvest energy from food and (iii) low-grade inflammation due to activation of toll-like receptors (TLR4), endotoxin and proinflammatory cytokine production (29, 30). Approximately 5% of ingested calories are lost in the stool and urine (31). Altered nutrient load over a three-day 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 three-day period and was associated with a ≈150 kcal increase in energy absorption.

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

3. Appetite control

There are two general definitions of appetite (36). The first relates to food preference, selection and intake, and the motivation to eat, whilst the second refers to qualitative and sensory aspects of food, including the impact of environmental stimulation. These eclipse homeostatic theories which suggested 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). Humans 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).

Appetite is controlled by multiple integrated physiological signals (See Figure 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 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 distention, while 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.

3,1 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 gastrointestinal tract and released in response to nutritional stimuli. Anorexigenic hormones include CCK, glucagon-like peptide-1 and -2 (GLP-1 and GLP-2), glucose-dependent insulinotropic polypeptide (GIP), oxyntomodulin, PP, peptide histidine isoleucine, peptide histidine valine, peptide YY and somatostatin)(51, 52) . Enteroendocrine (EE) cells represent less than one percent of the mucosal cell population, yet form the largest endocrine system in the human (53), and is populated by singly distributed enteroendocrine cells which release a very significant portion of appetite regulating hormones (54). (TABLE 1). EE cells 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 EE cell types in the colon are D cells, L cells and EnteroChromaffin (EC) cells (57). Whilst all cell types may be found along the colon, EC are the most abundant, and D cells the least, with a progressive increase in the proportion of L-cells along the caeco-rectal axis. As summarised in our review, these cells harbour peptide/hormones involved in appetitive regulation including PYY, GLP-1, GLP-2 and oxyntomodulin. Intriguingly the EC subclass also contain 5HT (serotonin) and reports suggest that as much as 95% of the body's 5HT 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 below.

SCFAs 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 (PYY) by activating two G-protein-coupled receptors (GPR41 and GPR43). EE carry free fatty acid receptors (FFARs) on their surface which have differential affinity for SCFAs and which signal the release of appetitive hormones from EEC (60). As components of the exometabolome, SCFAs 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 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 SCFA may modulate differentiation pathways on exit from the stem cell compartment (62). Taken together these data suggest two possible tiers of regulation of post-ingestive appetite by the exometabolome: (1) an acute response in terms of regulating release of anorectic hormones; and (2) an adaptive modulation of numbers of EEC and thereby available pools of appetite-regulatory hormones.

3,2 Impact of the exometabolome on post-absorbtive 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 and through pan-systemic 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 intake. Relatively recently the intestine has been identified as a site gluconeogenesis (distinguished as Intestinal GlucoNeogenesis – 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). This paper therefore also suggests emergent distinctions between the fates and activities of SCFA. Intestinally-produced glucose is transported to the HPV where it is directly sensed by sodium-coupled glucose co-transporter (66). Critically, in contrast to hepatic and renal gluconeogenesis, IGN 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, liver. The role of FFAR3 in non-gut tissue is reviewed elsewhere in this issue (67).

3.3 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 hypothesize 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 TLRs in the mucosa responding to the microbiome, and modulation of GABA-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.

4. 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 gastrointestinal tract (73). In a recent study, elite athletes had a significantly more diverse gut microbiota compared to non-athletic size matched

(high body mass index (BMI) ≈30) and age/gender matched (BMI <25) control groups (74). As the elite athlete group also consumed a significantly different diet, which provided more calories per day from carbohydrates, proteins and fat compared to the control groups, this 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 gastrointestinal 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 μ_{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 μ_{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 sections above, 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 longtundinal 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 opportunities for these microbial products to interact with the host epithelium, potentially increasing host energy harvest in the case of SCFAs, and elevating exposure to pro-inflammatory signalling and cytotoxic molecules.

6. 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 humans 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 humans 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 mircobiota in order to restore energy balance. Changes in gut microbiota composition have been observed after consumption of a calorie 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 humans (78-80). As such, intervention strategies are an attractive approach to appetite management through restoration of ecological balance in the gut.

7. Key conclusions and areas for future research

- Fibres are inconsistently defined and an oversight of the totality of nutrients entering the large bowel may be more informative
- 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.
- Most studies to date are associative and greater emphasis needs to be placed on longitudinal or prospective trials
- The relationship between the exometabolome and the host is dynamic and multifactorial, reductionist approaches are unlikely to yield an insight into health benefits.

Tables and Figure Legends

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

PYY, peptide YY; GLP-1, glucagon-like peptide 1; GLP-2, glucagon-like peptide 2.

Table taken from Gunarwardene Corfe & Staton CA (2011) with additional information from (81-83)

Figure 1 A chemical Ontology for "Fibre"

Accessed from ChEBI (www.chebi.ebi.ac.uk), 08.07.14

Figure 2 An alternative definition of "fibre"

Based on Ha et al (2000) this definition encompasses all material able to enter the colon (ICE – Ileo Caecal Effulent), as available for microbial metabolism. Some components are readily metabolised, some highly resistant to metabolism.

Fig 3 Tiers of appetite regulation by short-chain fatty acids

Figure 4 Intestinal Gluconeogenesis Pathway

Figure 5 Analogy between the Chemostat and the Colon

Chemostat image: chemistry.about.com, colon image www.clker.com

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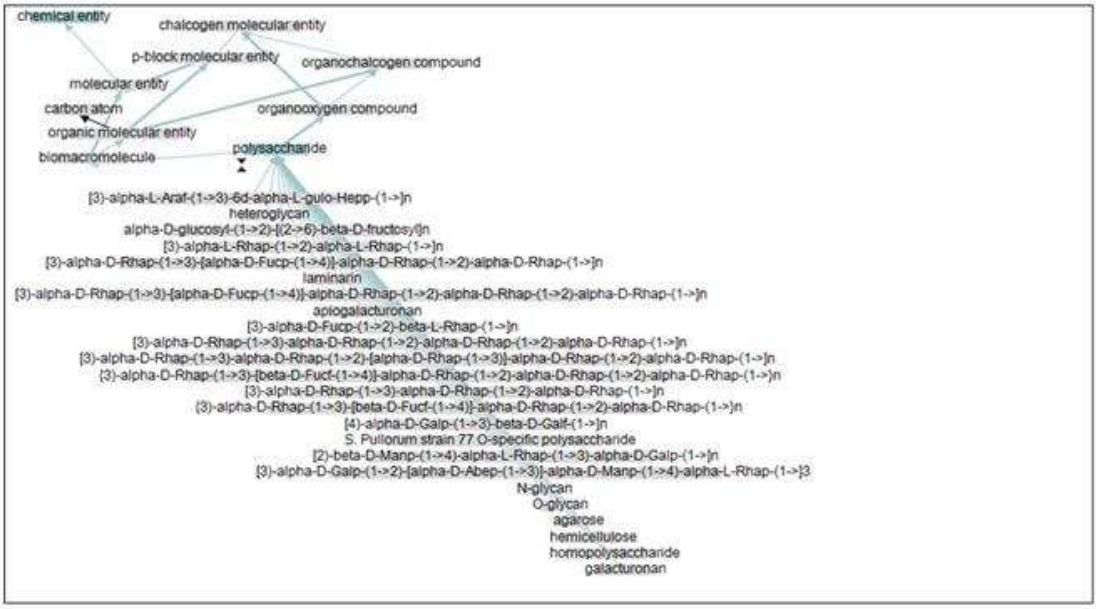
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S. Pullorum strain 77 O-specific polysaccharide
[2)-beta-D-Manp-(1->4)-alpha-L-Rhap-(1->3)-alpha-D-Galp-(1->]n
[3)-alpha-D-Galp-(1->2)-[alpha-D-Abep-(1->3)]-alpha-D-Manp-(1->4)-alpha-L-Rhap-(1->[3
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O-glycan
agarose
hemicellulose
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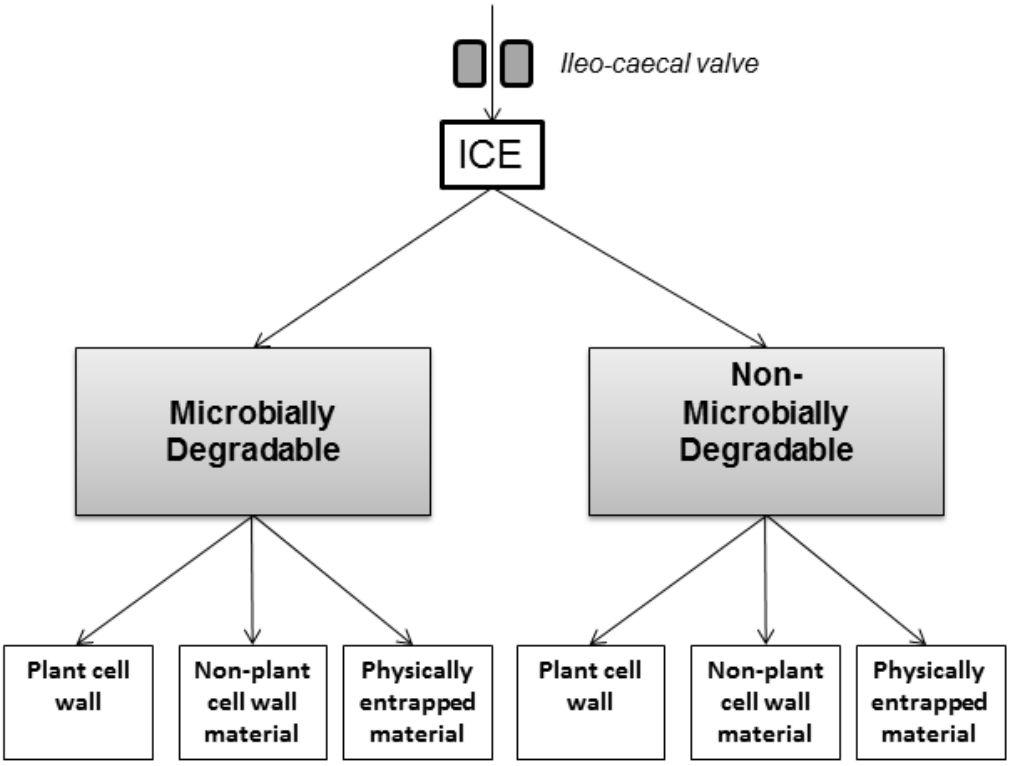
galacturonan


Ileo-caecal valve
ICE
Microbially Degradable
Non-Microbially Degradable
Plant cell wall
Non-plant cell wall material
Physically entrapped material
Plant cell wall
Non-plant cell wall material
Physically entrapped material

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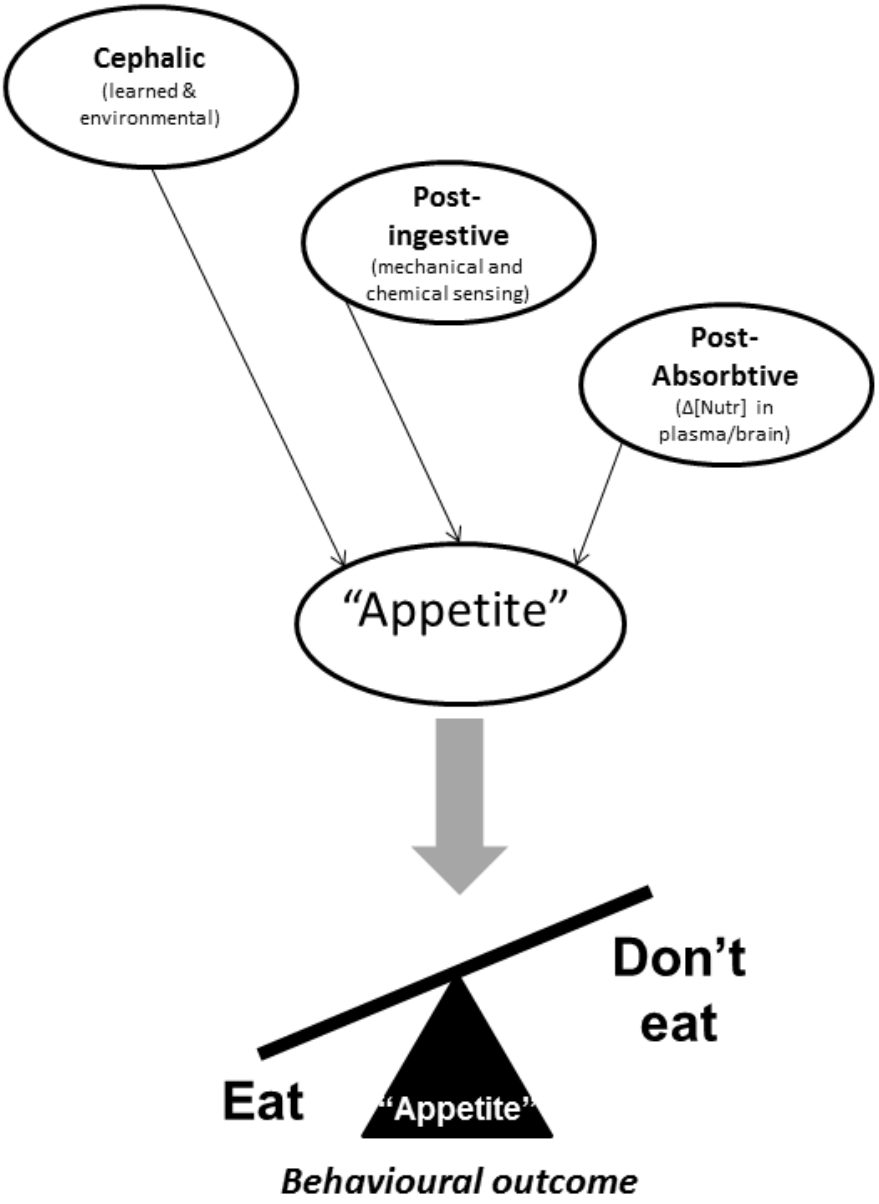
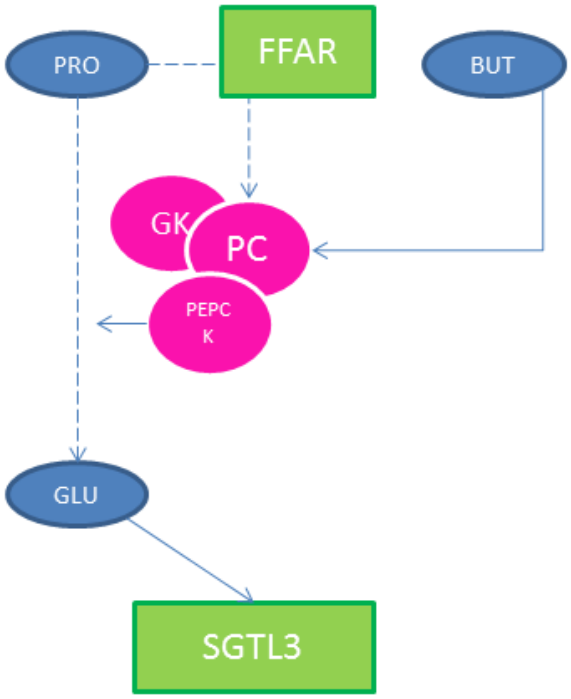

Cephalic
(learned & environmental)
Post-ingestive
(mechanical and chemical sensing)
Post-Absorbtive
(Δ[Nutr] in plasma/brain)
"Appetite"
Don't eat
Eat
"Appetite"
Behavioural outcome

540


PRO
FFAR
BUT
GK
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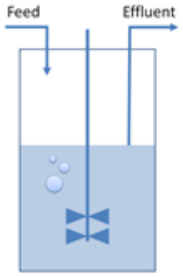
K
GLU
SGTL3

Chemostat

Continuous culture bioreactor

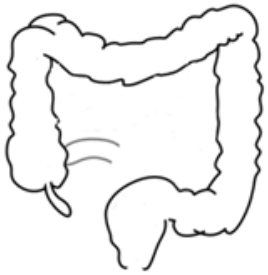


$$D = \frac{\text{Medium flow rate}}{\text{Culture volume}} = \frac{\text{F}}{\text{V}}$$

- Any given bacterial species will grow at a rate μ which is a function of D and the nature of the nutrient
- When μ_{max} is reached the species can no longer compete with D and will be progressively diluted from the system

Colon

Also a continuous culture bioreactor



- Increase faecal bulk
- F is a function of rate of ICE
- F is additionally a function of rate of absorption
- V is variable, but any given individual will have a Vmin and Vmax
- Insol Fibre will affect F and V and so have an effect on D
- Consequent selective pressure and impact upon the composition of the microbiome