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1 "Fibre, Gut Microbiome and Appetite"

2 **The multifactorial interplay of diet, the microbiome and** 3 **appetite control: current knowledge and future challenges**

4
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16

17 **Keywords:** fibre, microbiome, appetite, obesity, short-chain fatty acids

18

19 **Abstract**

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

34

35 1. Overview

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

52

53 2. Fibre /Dietary Residue

54 2.1 Scope of definitions of dietary fibre

55 Fibre is a component of diet which is highly complex and inconsistently defined. Approaches to the
56 definition vary from the biochemical, to the physiological, to the functional. The Englyst definition, for
57 example, is “non-starch polysaccharides” (8). This is in line with other definitions within nutrition,
58 although it is notable for the element of exclusion which places fibres in the general class of
59 polysaccharides outwith the subclass of starches. Fig 1 provides top-level indication of the potential
60 chemical complexity of this ontology (accessed from ChEBI 08.07.15). However, each endpoint within
61 this ontology masks further factors, including the degree of polymerisation: the nature and extent of
62 polymerisation of side-chains on any polysaccharide backbone. Against this rigid definition is the
63 Association of Official Agricultural Chemists (AOAC)-adopted version by Prosky (9), that fibres are
64 “remnants of plant cells resistant to digestion by human digestive enzymes”. This definition introduces a
65 physiological component, insofar as resistance to digestion implicates human physiology, but its relevance
66 to non-humans and humans with abnormal digestive capacity is questionable. For example, is “fibre”
67 different for animals with different profiles of digestive enzymes? Furthermore, what is the relationship
68 between fibre and personalised medicine? For example, in the case of an inborn error of metabolism
69 which may impair intraluminal digestion or absorption – is this definition personal, with each of us
70 potentially having a different profile of fibres? Finally, it introduces a source component, in this case
71 botanical, which raises the question of how fungi fit within this classification. The definition was further
72 extended to include an aspect of functionality in the following Scientific Advisory Committee on
73 Nutrition (SACN) statement:

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

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

86 This extended cynicism about mainstream definitions could be coupled to a simple, unifying observation:
87 bacteria cannot read research papers or position statements. The extent of compounds which reach the
88 colon has been demonstrated, *inter alia*, in studies of differentially diced almond skins, which were found
89 to yield a range of macro- and micro-nutrients (10). It can therefore be argued that the colon environment
90 is not solely nourished by fibres, but by the totality of the ileo-caecal effluente (ICE) - the material that
91 passes through the ileocaecal valve, whether intact or part-digested, whether of plant, animal or fungal
92 origin, whether polysaccharide or not. For the purposes of a review of interactions between fibres and the
93 microbiome, this definition facilitates the full scope of potential interaction between dietary factors and
94 the microbiome in understanding the production of the exometabolome. Our concept of ICE resembles
95 the definition of fibre proposed by Ha “Any dietary component that reaches the colon without being
96 absorbed in a healthy human gut” (11). The authors critically assimilate the overarching effects of fibre,
97 reproduced in Figure 2 – the division between fermentable and non-fermentable fibres. Fermentable
98 fibres are generally progressively degraded to metabolic endproducts including short-chain fatty acids

99 2,2 The nature of the exometabolome

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

109 3. Microbiome

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

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

127 Early indications that the gut microbiota was involved in obesity came when metabolically obese mice,
128 with a mutation in the leptin gene, were shown to have a significantly different microbiota compared to
129 mice without the mutation (23). Further investigation indicated that the ratio of Firmicutes to
130 Bacteroidetes in the gut microbiota of obese mice was shifted in favour of Firmicutes, whilst lean mice
131 were dominated by Bacteroidetes (24). In humans, the gut microbiota composition can respond to
132 changes in body weight and is altered in obese compared to non-obese individuals (18). Bacteroidetes
133 may be responsive to calorie intake because their levels increase when body weight is reduced following
134 a reduced calorie diet (25), although numerous human studies have failed to demonstrate a consistent
135 relationship between obesity and the ratio of Firmicutes to Bacteroidetes at both the phylum- and
136 species-level (26).

137 Hydrogen-producing Prevotellaceae and hydrogen-utilizing methanogenic Archaea were more abundant
138 in obese individuals suggesting a higher energy harvest in large intestine to hydrogen transfer between
139 bacterial and archaeal species (27). Changes in the composition of the gut microbiota have been linked
140 with (i) suppression of intestinal fasting-induced adipocyte factor (Fiaf), which is a contributing factor to
141 enhanced fat deposition (28), (ii) increased capacity to harvest energy from food and (iii) low-grade
142 inflammation due to activation of toll-like receptors (TLR4), endotoxin and proinflammatory cytokine
143 production (29, 30). Approximately 5% of ingested calories are lost in the stool and urine (31). Altered
144 nutrient load over a three-day period induced changes in the gut microbiota in both obese and non-obese
145 individuals, despite statistically significant differences in the composition of the lean and obese
146 microbiome at baseline under a weight maintaining diet (32). In the case of lean subjects, a 20% increase
147 in Firmicutes (and a corresponding decrease in Bacteroidetes) was observed over the three-day period and
148 was associated with a ≈ 150 kcal increase in energy absorption.

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

153

154 **3. Appetite control**

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

166 Appetite is controlled by multiple integrated physiological signals (See Figure 3). Short-term signals help
167 regulate meal initiation and termination whereas long-term, humoral signals play a central role in body
168 weight regulation (43). This conceptual framework for examining the impact of feeding is continually
169 updated to represent an increasing number of factors encompassing peripheral physiological and
170 metabolic events, and brain responses that play important roles in appetite control (44). The GI tract
171 responds to feeding in three integrated phases: cephalic, post-ingestive and post-absorptive, all of which
172 depend on parasympathetic nerve transmission. The cephalic phase occurs at the point of food selection
173 and early ingestion, and is thus stimulated by conditioned processes and organoleptic factors (45, 46). It
174 is held that post-ingestive satiation signals arise largely from mechanical distention, while signals from the
175 GI tract derive predominantly from the chemical effects of food (47). In contrast, post-absorptive effects
176 are the result of interplay between hormones and the hypothalamic region of the brain that respond to
177 fluctuating concentrations of nutrients in the portal vein, plasma and brain.

178 *3.1 Impact of the exometabolome on post-ingestive appetite regulation*

179 Landmark human studies have shown intestinal nutrient infusions can reduce food intake with rapid
180 effects (48-50), indicating that satiation signals must originate from the gut as well as post-absorptively.
181 Numerous hormones, neurotransmitters and peptides stimulate orexigenic or anorexigenic responses.
182 Many peptide hormones are produced in the gastrointestinal tract and released in response to nutritional
183 stimuli. Anorexigenic hormones include CCK, glucagon-like peptide-1 and -2 (GLP-1 and GLP-2),
184 glucose-dependent insulinotropic polypeptide (GIP), oxyntomodulin, PP, peptide histidine isoleucine,
185 peptide histidine valine, peptide YY and somatostatin(51, 52) . **Enteroendocrine** (EE) cells represent less
186 than one percent of the mucosal cell population, yet form the largest endocrine system in the human (53),
187 and is populated by singly distributed enteroendocrine cells which release a very significant portion of
188 appetite regulating hormones (54). (TABLE 1). EE cells have a characteristic flask-shaped morphology
189 and have been divided into at least sixteen cellular subtypes based on the major products they produce
190 and secrete (55), although this model is contested and a continuum of cell types has also been proposed
191 (56).

192 The primary EE cell types in the colon are D cells, L cells and EnteroChromaffin (EC) cells (57). Whilst
193 all cell types may be found along the colon, EC are the most abundant, and D cells the least, with a
194 progressive increase in the proportion of L-cells along the caeco-rectal axis. As summarised in our review,
195 these cells harbour peptide/hormones involved in appetitive regulation including PYY, GLP-1, GLP-2
196 and oxyntomodulin. Intriguingly the EC subclass also contain 5HT (serotonin) and reports suggest that as
197 much as 95% of the body's 5HT may exist in the gut (58) Serotonin has been implicated in appetitive
198 regulation, mood control and regulation of gut transit. This underwrites plausible links between luminal
199 content, motivation to eat and wider aspects of regulation of colorectal content through modulation of
200 transit time. These factors are explored in greater detail below.

201 SCFAs are important signalling components within the gut-brain axis, the system of communication
202 between the gut and the brain (19, 59) which interacts directly with gut endocrine cells, and stimulates
203 secretion of peptide YY (PYY) by activating two G-protein-coupled receptors (GPR41 and GPR43). EE
204 carry free fatty acid receptors (FFARs) on their surface which have differential affinity for SCFAs and
205 which signal the release of appetitive hormones from EEC (60). As components of the exometabolome,
206 SCFAs therefore act as key molecules governing the sensing-signalling pathway linking luminal
207 metabolism to appetite regulation.

208 Our group have recently identified a further plausible mechanism of action. A significant body of
209 literature suggests butyrate is a potent regulator of numbers of proliferating cells in the colon crypt. We
210 recently demonstrated an inverse association between SCFA and the numbers of EEC cells in the crypt

211 (61). Mathematical modelling suggests SCFA may modulate differentiation pathways on exit from the
212 stem cell compartment (62). Taken together these data suggest two possible tiers of regulation of post-
213 ingestive appetite by the exometabolome: (1) an acute response in terms of regulating release of anorectic
214 hormones; and (2) an adaptive modulation of numbers of EEC and thereby available pools of appetite-
215 regulatory hormones.

216 *3.2 Impact of the exometabolome on post-absorptive appetite regulation*

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

223 Gluconeogenesis has until relatively recently been viewed as a primarily hepatic and renal phenomenon,
224 and is not positively associated with health, reflecting excess energy intake. Relatively recently the
225 intestine has been identified as a site gluconeogenesis (distinguished as Intestinal GlucoNeogenesis –
226 IGN) (64). IGN is regulated by both butyrate and propionate. Butyrate acts to govern the levels of IGN
227 enzymes in the mucosa. In contrast propionate is both a substrate for IGN and is a regulator of IGN
228 enzyme activity mediated *via* FFAR3 signalling (Fig 4) (65). This paper therefore also suggests emergent
229 distinctions between the fates and activities of SCFA. Intestinally-produced glucose is transported to the
230 HPV where it is directly sensed by sodium-coupled glucose co-transporter (66). Critically, in contrast to
231 hepatic and renal gluconeogenesis, IGN associated with positive health outcomes (65) .

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

235 *3.3 Impact of the exometabolome on cephalic phase of appetite regulation*

236 The impact of exometabolites upon cephalic phase of appetite has not been well explored however it is
237 reasonable to hypothesize that it does contribute to the wider mechanisms of appetite control as
238 precedents have been shown in microbiome-mood interactions. For example: perturbations of the gut
239 flora have been associated with schizophrenia and depression (68, 69); probiotic interventions in mouse
240 models have demonstrated anxiolytic potential of microbial intervention (70); probiotic interventions
241 have also shown impact upon brain activity (71) and on cognitive outcome (72). Recent reviews have
242 suggested potential mechanisms of action, including modulation of afferent signalling by SCFA, cytokine-
243 mediated responses triggered through TLRs in the mucosa responding to the microbiome, and
244 modulation of GABA-mediated signalling (15). As a strong evidence-base is emerging for a role of the
245 microbiome and exometabolome in governance of mood and cognition, it seems likely that this will in
246 time extend through to cephalic phase appetite control.

247

248 **4. Modification of the microbiome by alteration of transit (the chemostat analogy)**

249 Although obesity and obesity-related disorders have been linked with alterations in the gut microbiota,
250 less attention has been directed towards investigating lifestyle aspects of obesity, such as exercise and diet,
251 and their effect on the microbial and physical environment of the gastrointestinal tract (73). In a recent
252 study, elite athletes had a significantly more diverse gut microbiota compared to non-athletic size matched

253 (high body mass index (BMI) ≈ 30) and age/gender matched (BMI < 25) control groups (74). As the elite
254 athlete group also consumed a significantly different diet, which provided more calories per day from
255 carbohydrates, proteins and fat compared to the control groups, this study suggested that both diet and
256 exercise were driving factors in changing gut microbial diversity. Exercise has also been shown to
257 decrease transit time, particularly through the descending colon (74, 75). Previous reports have suggested
258 however, that physical activity does not necessarily improve overall gastrointestinal transit (76).

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

271 We therefore argue that a contributing longitudinal effect of high fibre intakes, or high physical activity,
272 or the combination thereof is the modification of the microbiome by exerting a specific selective
273 pressure. Contrastingly, excessive slow values for dilution rate, D, will provide opportunities for these
274 microbial products to interact with the host epithelium, potentially increasing host energy harvest in the
275 case of SCFAs, and elevating exposure to pro-inflammatory signalling and cytotoxic molecules.

276

277 6. Summary and future directions

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

297 **7. Key conclusions and areas for future research**

- 298
- 299 Fibres are inconsistently defined and an oversight of the totality of nutrients entering the large
300 bowel may be more informative
 - 301 Perturbations in the microbiome associate with obesity and increased energy harvest. The
302 relationship between the diet and microbiome and host health is mediated considerably by the
303 exometabolome.
 - 304 Most studies to date are associative and greater emphasis needs to be placed on longitudinal or
305 prospective trials
 - 306 The relationship between the exometabolome and the host is dynamic and multifactorial,
reductionist approaches are unlikely to yield an insight into health benefits.

307

308

309

Tables and Figure Legends

310 **Table 1: The secretory products of enteroendocrine cells of the colon and rectum and their**
311 **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

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

313

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

315

316

317

318

319 **Figure 1 A chemical Ontology for “Fibre”**

320 Accessed from ChEBI ([www.ebi.ac.uk](http://www.ebi.ac.uk/chebi)), 08.07.14

321

322 **Figure 2 An alternative definition of “fibre”**

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

326

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

328

329 **Figure 4 Intestinal Gluconeogenesis Pathway**

330

331 **Figure 5 Analogy between the Chemostat and the Colon**

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

333

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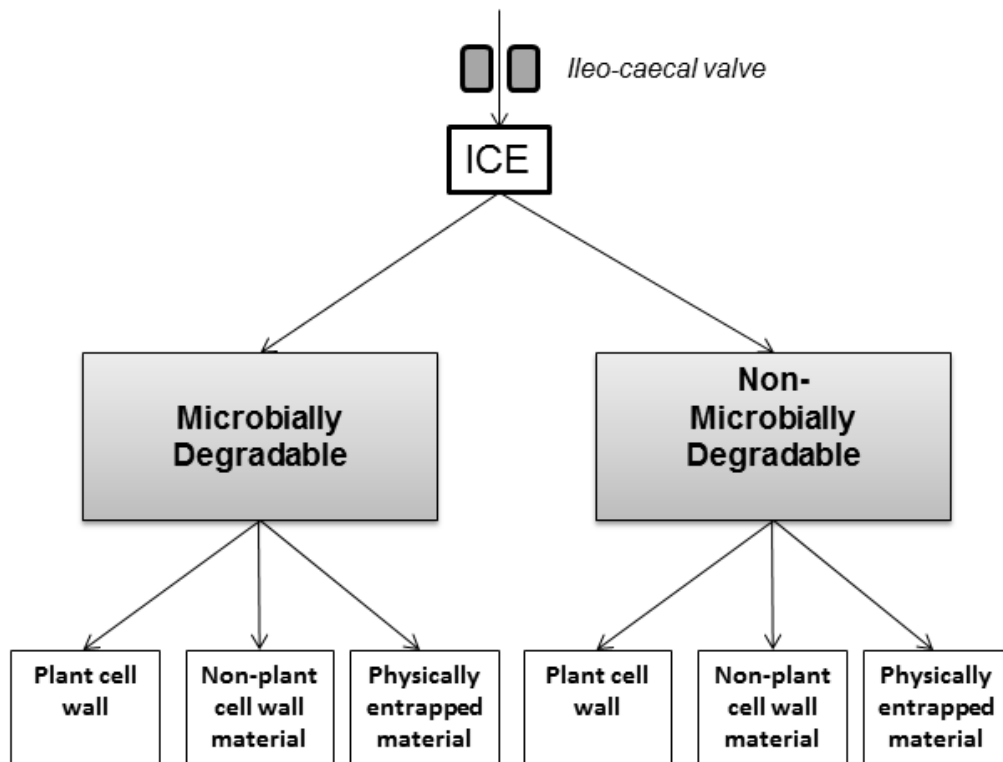
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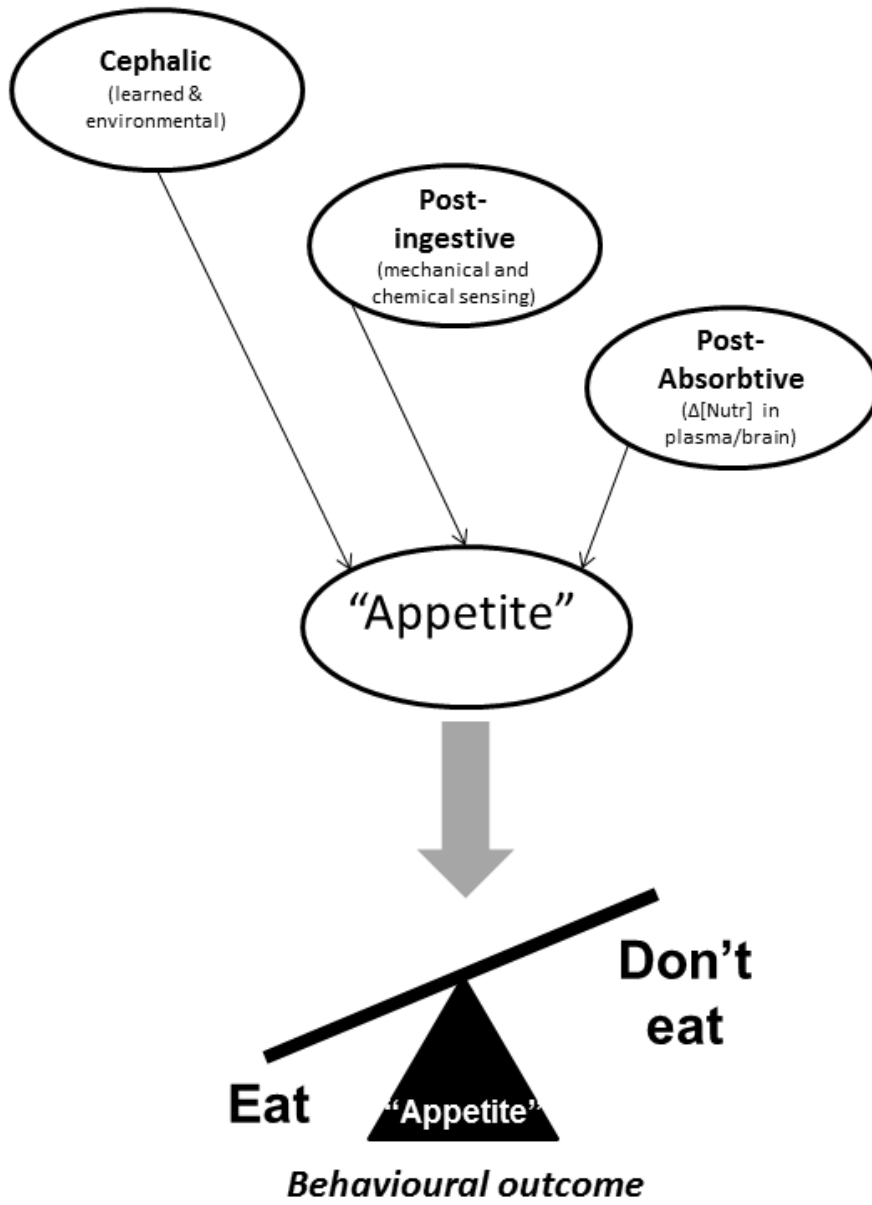
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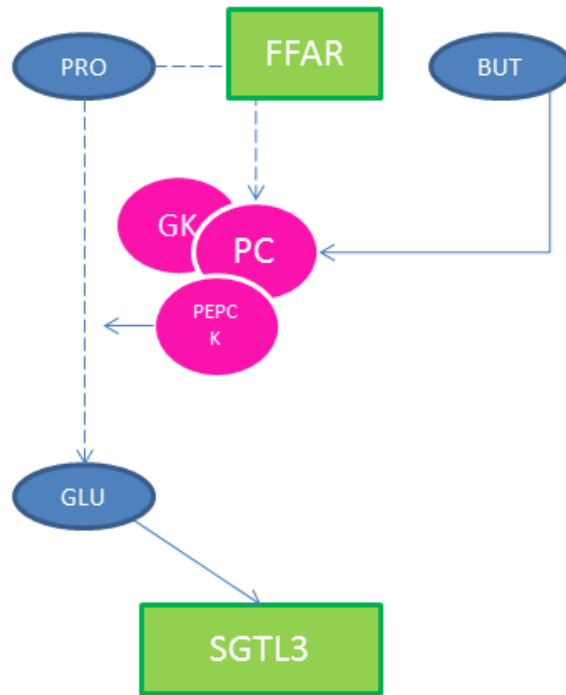
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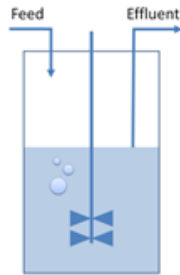






Chemostat

Continuous culture bioreactor



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

- 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 V_{\min} and V_{\max}
- 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