The Microbiota-Gut-Brain Axis in Obesity

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Specific contributions

HS, CT, TD and JC significantly contributed to the manuscript concept, structure and writing of the manuscript.

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Keywords

Intestinal microbiota, microbiota-gut-brain axis, metabolism, appetite, obesity, lifespan, metabolites, immune modulation, neuroendocrine factors, microbiota-based therapies.

Abstract

Growing evidence points to changes in microbial diversity and composition being associated with a number of disease states including obesity and behavioral disorders. The obese microbiota alters host energy harvesting, insulin resistance, inflammation and fat deposition. In addition, the intestinal microbiota has been shown to regulate metabolism, adiposity, homeostasis and energy balance as well as central appetite and food reward signaling, which together play crucial roles in obesity. Moreover, certain strains of bacteria and their metabolites may target the brain directly via vagal stimulation or indirectly through immune-neuroendocrine mechanisms. Therefore, the gut microbiota is becoming a target for the development of new anti-obesity therapies. Further investigations are needed to elucidate the intricate gut microbiota-host relationship and the potential of gut microbiota-targeted strategies, such as dietary interventions and faecal microbiota transplantation, as promising metabolic therapies to maintain a healthy weight throughout the lifespan.

Search Strategy and selection criteria

The aim of this review was to identify studies investigating the effects of the gut microbiota on host metabolism and central appetite regulation in the context of obesity. Thus, references were identified through an extensive search in PubMed, Google Scholar and Web of Sciences online databases, with the key search terms of [obesity], [microbiota], [microbiome], [metabolic syndrome] and [appetite] since 2000. Only papers published in English were reviewed. The final reference list was generated based on the relevance to the broad scope of this Review and in accordance with the Journal’s reference limits.

1. Introduction

Hippocrates, the father of modern medicine, famously said: "*All disease starts in the gut*". The last two decades have seen an explosion of research supporting this concept. The human intestine harbors tens of trillions of microorganisms, including archaea, bacteria, viruses, phages, fungi, protists and nematodes, but dominated by bacteria from the phyla *Firmicutes* and *Bacteriodetes.* This gut microbiota ecosystem is established after birth following transfer of maternal bacteria as well as bacteria from the environment, and continues to develop until adulthood (for review see [1]).

Despite it being ignored for years, the gut microbiota is one of the largest components of our body, weighing approximately 1-2kg and contain greater than 100-fold more genes compared to the human genome alone [2]. Moreover, commensal bacteria in our gut have established a crucial symbiotic relationship with our bodies throughout evolutionary history exerting a plethora of protective and structural effects on the intestinal mucosa. Thus, the gut bacteria are becoming increasingly recognized as a key regulator of host physiology and pathophysiology with an undeniable role towards health and disease (for review see [3]). Indeed, alterations in the human gut microbiota composition have been shown in metabolic conditions such as obesity and diabetes (for review see [3]) and eating disorders as well as in stress-related neuropsychiatric disorders including depression (for review see [4]) and anxiety (for review see [5]) which are also characterized by changes in eating behavior. Moreover, the gut microbiota regulate fat storages [6] and has the capacity to harvest energy from the diet [7]. Several studies have also shown that the intestinal microbiota also affect others physiological processes such as inflammation, insulin and glucose metabolism as well as hepatic lipid metabolism (for review see [8]). Furthermore, gut bacteria can directly impact the central nervous system (CNS) via modulation of different endocrine pathways of the microbiota-gut-brain axis, e.g. via glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) signaling or even activating reward pathways (for review see [9]).

Taking together, a healthy gut microbiota is of crucial importance for proper metabolic function and homeostasis, which significantly benefits the host in exchange for the privilege of living and proliferating in the intestinal habitat. Alterations in microbiota composition, especially early in life may prime for obesity and diabetes, through significant modification of the host metabolism and affect homeostasis and central appetite mechanism [10]. Thus, modulation of the intestinal microbiota by dietary interventions, including pre-and probiotics, or faecal transplantation may have potential as novel anti-obesity strategies. It should be noted that a growing body of evidence suggests that the success of bariatric surgery is due to its effects on the microbiota (**Box 1**) [11]. This may have high impact in society nowadays as obesity and its co-morbidities within the metabolic syndrome (i.e. type II diabetes, cardiovascular disease and a pro-inflammatory phenotype), are reaching epidemic proportions and are serious health concerns worldwide, which urgently need to be addressed [12, 13].

In addition to metabolic changes, obesity is also a disorder of brain and behavior. A growing body of research is focusing on the ability of the microbiome to affect various brain processes and modify behaviors relevant to both the homeostatic and hedonic aspects of food intake [14]. Here, we review the growing promise of the gut microbiota as a key regulator of host metabolism, central appetite regulation and food reward and its implications in metabolic disorders such as obesity. We summarize current literature on potential mechanism by which the intestinal microbiota affects central appetite regulation and energy metabolism, through alterations of gut-brain axis signaling. We review how certain bacterial strains may contribute or protect towards metabolic disease via modification of host metabolism and/or appetite regulation, while also addressing how faecal microbiota transplantation (FMT), bariatric surgery and dietary interventions, including pre- and probiotics, may be used as promising novel metabolic therapies in clinical practice in the management of obesity.

2. The obese microbiota

One of the earliest key findings implicating the intestinal microbiota role in energy balance originated from germ-free mice, which completely lack any intestinal microbiota from birth. These mice are protected against obesity and are significantly leaner than normal control mice despite consuming more calories [6]. In addition, germ-free mice have altered plasma lipid metabolic markers and lower levels of the circulating hunger hormone ghrelin and adipose factor leptin, indicative of energy deficits [15]. On the other hand, specific alterations in gut microbial composition have been linked with obesity. Thus, a wider variety of Bacteroidetes, which break down bulky plant starches and fibers as an energy source, was found in lean individuals, while an increase in the phylum Firmicutes was found in obese individuals [16]. Furthermore, despite large variations in composition amongst individuals, a core human microbiome was found to be altered in obese individuals [17]. Finally, the obese phenotype, was transmittable via the intestinal microbiota alone in germ-free mice [18] or humans [19]. Crucially, the transferred obese phenotype was reversed following co-housing with mice transplanted with the lean microbiota [19]. These findings demonstrate the transmissible, rapid and modifiable nature of interactions between diet and the microbiota in relation to obesity and the metabolic syndrome.

More recently the link between microbiota and obesity was challenged in a meta-analysis where datasets from ten different previous studies were pooled by using a random-effect model and no significant associations were observed for the ratio of Bacteroidetes and Firmicutes or their individual relative abundance [20]. The authors demonstrated that most of the current studies have not sufficient power to detect a 5% difference in diversity as well as a large interpersonal variation and insufficient sample sizes

Box 1. Bariatric surgery and its effects on the gut microbiota.

Bariatric surgery is an intervention indicated for severe obesity and the only treatment to date that leads to substantial and sustained weight loss. Different kinds of bariatric surgeries procedures are available such as adjustable gastric banding (AGB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD)[1]. Human and animal studies have shown that RYGB reduces adiposity and improves insulin sensitivity as well as the hormonal (increased GLP-1 and PYY) and inflammatory status and increases the pool of bile acids[1]. Moreover, RYGB also affects the gut microbiota composition leading to an increased diversity[1]. For example, although with differences across studies, increased abundance of *Gammaproteobacteria* and Verrucomicrobia (*Akkermansia*) as well as decreased Firmicutes[2] abundance have been reported in humans and rodent bariatric studies[1]. Moreover, faecal microbiota transplantation (FMT) from mice that underwent RYGB into germ-free mice resulted in weight loss and decreased fat mass in the recipient animals potentially due to altered microbial production of short-chain fatty acids with increased propionate levels and decreased acetate levels[3]. Therefore, bariatric surgery leads to specific changes in the gut microbiota resulting in a different short-chain fatty acids (SCFA) composition and thus influencing host metabolism including gut hormone secretion and insulin sensitivity. These effects may be central to the success of RYGB in treating obesity, metabolic syndrome and diabetes. For review see[1,4].

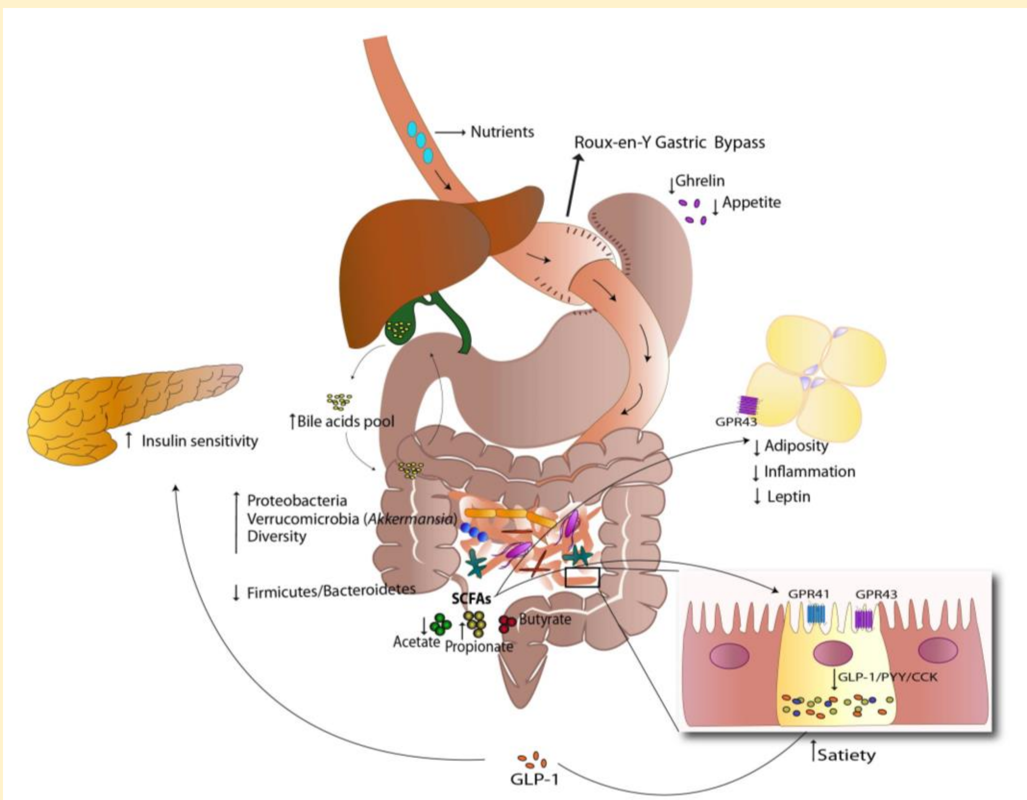

Figure 1. Roux-en-Y gastric bypass surgery effects on the gut microbiota and its metabolic outcomes

1. Aron-Wisnewsky, J. and K. Clement, The effects of gastrointestinal surgery on gut microbiota: potential contribution to improved insulin sensitivity. Curr Atheroscler Rep, 2014. 16(11): p. 454.

2. Zhang, H., et al., Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci U S A, 2009. 106(7): p. 2365-70.

3. Liou, A.P., et al., Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. Sci Transl Med, 2013. 5(178): p. 178ra41.

4. Berthoud, H.R., The vagus nerve, food intake and obesity. Regul Pept, 2008. 149(1-3): p. 15-25.

Complex interactions between other environmental factors, host genetics and the gut microbiota play a critical role in the pathophysiology of obesity and diabetes. Indeed, a recent study in mice demonstrated that alterations in the gut microbiota following environmental reprogramming ameliorated the development of metabolic syndrome in different mice strains (obesity/diabetes-prone C57Bl/6J mice, obesity/diabetes-resistant 129S1/SvImJ, and obesity-prone but diabetes-resistant 129S6/SvEvTac)[21]. Moreover, a fascinating twin study showed that host genetics influence the gut microbiota composition as well as host metabolism [22]. Thus, monozygotic twins showed a more similar gut microbiota composition than dizygotic twins and were enriched in certain taxa including *Christensenellaceae minute*. Moreover, an obese-associated microbiome enriched *C. minute* and transplanted to germ-free mice, reduced weight gain and altered the microbiome of the recipient mice[22].

3. Microbiota-driven mechanisms of metabolism and appetite regulation

Although the gut microbiota is a contributing and potential causal factor to the development of obesity and the metabolic syndrome, the exact mechanisms underlying this relationship are unclear. Nevertheless, it is known that the intestinal microbiota produce different bioactive metabolites in a diet-dependent manner, including short-chain fatty acids (SCFA) and conjugated fatty acids amongst others (for review see[23]). These microbiota-derived metabolites have been shown to have peripheral effects, as well as epigenetic modulation capability, modifying host metabolism and the central regulation of appetite via direct or indirect mechanisms (**Figure 2**) (for review see[9, 14]).

3.1 Effect of microbiota on peripheral metabolic signaling

Intestinal microbiota has been shown to influence host peripheral metabolic function. Metagenomics and biochemical analysis in genetically obese mice (*ob/ob*, leptin deficient mice) revealed that an obese microbiota increases the efficiency of calorie harvest from ingested foods and affects energy balance by influencing how this harvested energy is used and stored [7]. Thus, an obese microbiota provide to the human host a more efficient capability to extract more energy from otherwise indigestible carbohydrates and proteins compared to the lean-associated gut microbiota, via increased production of different primary fermentation enzymes and nutrients transporters [24]. However, it has also been shown that the proportion of the major phyla Firmicutes and Bacteroidetes are unrelated to markers of energy harvesting, highlighting that this relationship may be more complex than previously considered [25].

Furthermore, the gut microbiota has been shown to influence others obesity-associated factors such as high fasting glucose levels (hyperglycemia) and insulin resistance (for review see [26]). Indeed, germ-free mice show a resistance to the development of these high-fat diet-induced metabolic complications[27] that is abolished upon faecal microbiota transplantation from conventionally raised mice[6]. One of the potential mechanisms underlying the effect of the gut microbiota on the glucose and insulin homeostasis may be their impact on the composition and relative abundance of bile acids species (for review see[28]). Reduced bile acid levels in the gut has been associated with bacterial overgrowth and inflammation (for review see[28]). Hence, certain bacteria in the gut utilize bile acids and their conjugates leading to activation in intestine and liver of the bile acid receptors farnesoid X receptor (FXR) and the Takeda G-protein-coupled receptor 5 (TGR5), which are essential receptors for maintaining glucose tolerance and insulin sensitivity (**Figure 2**) (for review see[]). Thus, activation of TGR5 leads to improvement of liver function and glucose tolerance in obese mice by regulating intestinal GLP-1 production [30] while FXR deficiency in leptin-deficient mice has been shown to protect against obesity and improves insulin sensitivity [31]. Indeed, obese and type 2 diabetic patients have altered bile acid metabolism (for review see [32]). In addition, administration of bile acids, in both human and animal studies, have shown to improve glycemic control [33]). Furthermore, the impact of the gut microbiota on serotonin metabolism may also influence host glucose homeostasis (for review see [34]). Thus, pharmacologic stimulation of serotonin 5-HT$_{1B}$ or 5-HT$_{4}$ receptors has been shown to increase plasma active GLP-1 levels independently of feeding and improves glucose tolerance under the dipeptidyl peptidase-4 inhibition in mice [35].

The gut microbiota may also influence fat storage and hepatic lipid metabolism. Hence, Backhed and colleagues showed that fasting-induced adipocyte factor (Fiaf), a circulating lipoprotein lipase inhibitor, is selectively suppressed by intestinal bacteria inducing the deposition of triglycerides in adipocytes [6]. Moreover, bacteria in the gut affects the bioavailability of choline, which is an essential nutrient for the synthesis of one of the major components of the very-low-density lipoproteins (VLDL), affecting the storage of triglycerides in the liver [36]. More recently, gut microbiota-mediated activation of the bile acid FXR receptor has been shown to increase adiposity [37].

The gut microbiota has also been associated with inflammation in the context of obesity. Thus, increased plasma levels of lipopolysaccharide (LPS), an endotoxin present in the cell wall of gram-negative bacteria, leads to the development of metabolic endotoxemia inducing a strong immune system respond and contributing to the obesity-related low-grade inflammation (for review see [38]. Dietary fat seems to be crucial in this process as it increases intestinal LPS absorption through its incorporation into chylomicrons. Moreover, impaired integrity of the intestinal barrier may also contribute to this metabolic endotoxemia (for review see [38]). However, certain gut bacteria may prevent this endotoxemia by increasing SCFA levels and thus protecting the intestinal barrier integrity via increasing the mucus layer as well as tight junction protein expression (for review [39]).

3.2 Microbiota and obesity –From Gut to Brain

Appetite, food intake and energy balance are centrally regulated by a complex network of neuroendocrine factors and their receptors which mediate the bidirectional communication between the gastrointestinal tract and the brain (**Figure 2**) (for review see [14]). Thus, the presence of nutrients in the GI tract upon meal ingestion leads to complex neural and hormonal signaling to the brain to inform of the ongoing change in the nutritional status. This signaling is mediated by afferent nerve fibers from the autonomic nervous system, such as the vagus nerve, that project information from the gut to the nucleus tractus solitarius (NTS) in the brain as well as by effector fibers that project to the smooth muscles of the gut. Information from the NTS is distributed then to the hypothalamus where energy balance, appetite and food intake is regulated in the neurons of the arcuate nucleus (ARC) (for review see [40]). ARC contains orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) as well as anorexigenic peptides cocaine amphetamine-related transcript (CART) and pro-opiomelanocortin (POMC) containing neurons (**Figure 2**) (for review see [40]).

This central role of the vagus nerve in appetite signaling is supported by studies that shown that vagotomy in animal models resulted in a loss of anorexigenic hormone signaling and therefore, in overfeeding and weight gain [41]. However, results from human studies are more contradictory and it is still unclear how vagus nerve stimulation affects eating behaviors (for review see [42]. In addition, gut peptide secretion from enteroendocrine cells (EECs) also contribute to this nutritional status signaling from the gut to the brain via afferent nerve fibers as well as by direct secretion into the circulatory system (for review see [14]). Certain bacterial strains have shown the capability to modify gut hormone secretion, including PYY, GLP-1, leptin and ghrelin, having an impact on appetite and satiety via hypothalamic neuroendocrine pathways (**Figure 2**) (for review see [43, 44]). Indeed, microbiota-derived metabolites, such as SCFAs, have been shown to bind to receptors on ECCs modifying the release of enteric hormones into the systemic circulation [45]. Hence, non-digestible carbohydrates fermentation by the intestinal microbiota has been shown to increase the production of these SCFAs and eventually the secretion of different gut hormones in both animal and human studies (for review see [43]).

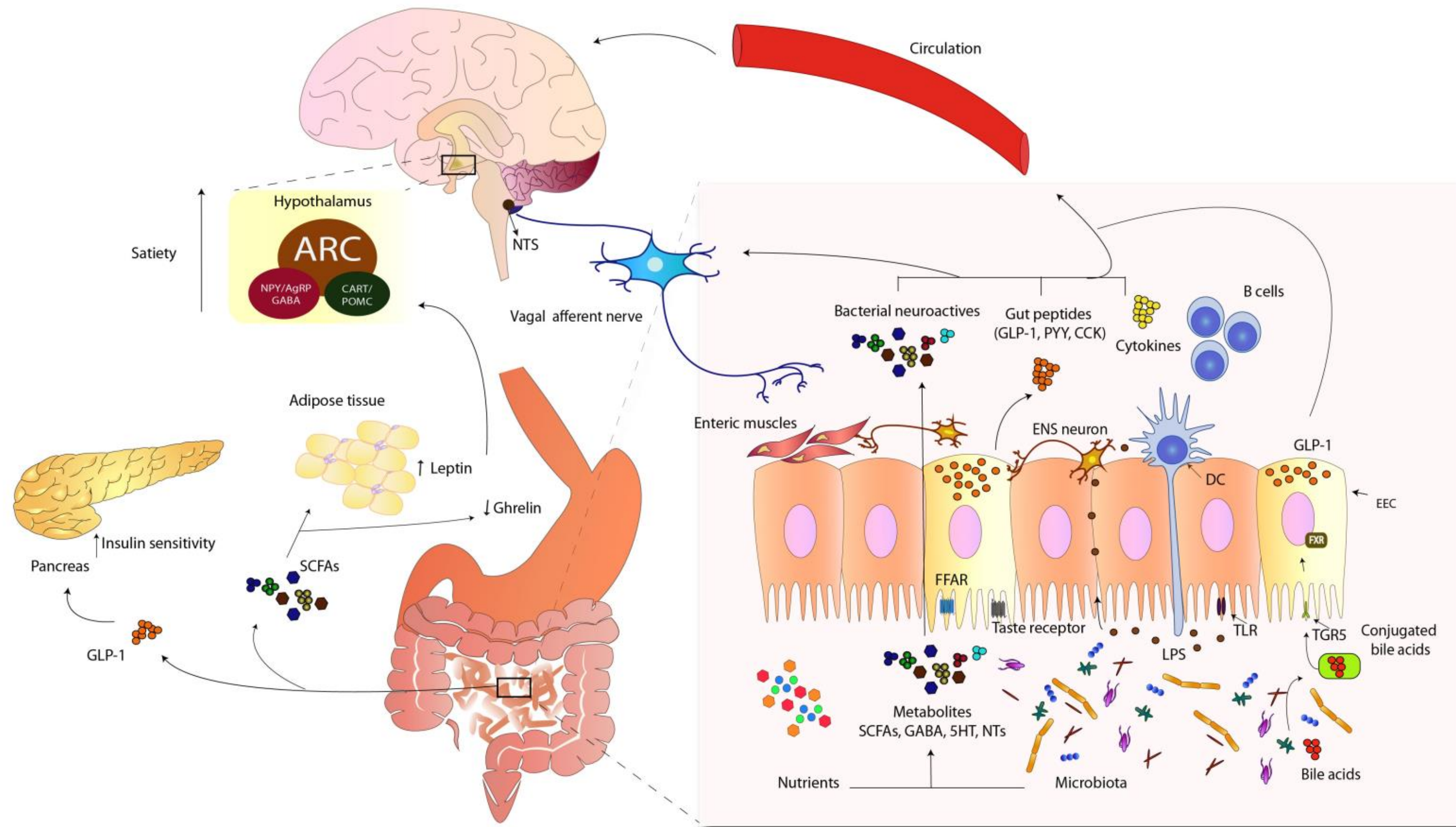

Figure 2. Microbiota-driven mechanisms of metabolism and appetite regulation. Intestinal microbes convert dietary nutrients into metabolites such as short-chain fatty acids (SCFAs), gamma-Aminobutyric acid (γ-Aminobutyric acid) (GABA), serotonin (5-HT) and others neurotransmitters (NTs) which have different peripheral and central effects modifying the host metabolism and the central regulation of appetite directly via vagal stimulation or indirectly through immune-neuroendocrine mechanisms. Enteroendocrine cells (EEC) are activated by these microbial-derived metabolites via activation of different receptors (e.g. fatty acid receptors (FFAR) and taste receptors) leading to the production of gut hormones such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and cholecystokinin (CCK). These gut hormones signal from the gut to the nucleus tractus solitarius (NTS) in the brain via the vagus nerve and as well as by direct secretion into the circulatory system. Information from the NTS is distributed then to the arcuate nucleus (ARC) in the hypothalamus where appetite and energy balance is regulated. ARC contains orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) as well as anorexigenic peptides cocaine amphetamine-related transcript (CART) and pro-opiomelanocortin (POMC) neurons. Moreover, gut microbes may also utilize bile acids and their conjugates leading to activation of the BA receptors farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5) and to an increased GLP-1 secretion by EECs. GLP-1 released in the gut is also essential for maintaining glucose tolerance and insulin sensitivity. Moreover, microbial-derived metabolites may also lead to others peripheral effects such as increased leptin production by the adipose tissue or decreased ghrelin production in the stomach. In addition, gut microbiota has also been associated with inflammation via released of lipopolysaccharide (LPS) that leads to the activation of immune cells, such as B cells or dendritic cells (DC) and cytokines production.

In addition, acetate, the main SCFA secreted by intestinal bacteria, have shown to directly suppress appetite via central hypothalamic mechanisms [46]. However, more recently it has been shown that increased levels of acetate by an altered microbiota leads to parasympathetic nervous system activation promoting glucose-stimulated insulin secretion, increased ghrelin secretion and obesity [47]. Moreover, absence of microbiota in germ-free mice has been shown to result in marked decreases in expression of intestinal satiety peptides [15]. In addition, these germ-free mice showed increased expression of oral fat taste receptor, the fatty acid translocase receptor (FAT), resulting in an increased caloric intake from fats [15]. These oral receptors transmit information from the taste papillae via nerve fibers to the NTS in the brainstem (for review see [48]). Moreover, in ECCs, different taste receptors, such as sweet, fat, bitter and umami receptors, are expressed and their activation lead to secretion of GLP-1, cholecystokinin (CCK) and ghrelin (for review see [48]). Hence, modulation of taste receptors may also be involved in the impact of the gut microbiota on the host's appetite control. Indeed, others studies with mice lucking microbes also showed alteration in others taste receptors such as the intestinal sweet signaling protein type 1 taste receptor 3 (T1R3) leading to increased consumption of nutritive sweet solutions [49].

Moreover, gut bacteria have even been shown to produce neuroactive metabolites including serotonin and γ-aminobutyric acid (GABA) (for review see [50]) which have been shown to influence the central control of appetite [51, 52]. Thus, serotonin mediates appetite suppressant effects by modulation of melanocortin neurons, which have a key role in the central control of body weight homeostasis [53, 54]. GABA, the main inhibitory neurotransmitter in the central nervous system and one of the main neurotransmitters involved in hypothalamic synaptic transmission, has been shown to stimulate feeding and evidences indicate that the synaptic release of GABA by AgRP-expressing neurons in the hypothalamic arcuate nucleus is required for normal regulation of energy balance (for review see [52]).

3.3 Microbiota & Behaviour: Mood, reward and feeding-related pathways.

In addition to the above-mentioned mechanisms, gut microbes may also influence the host feeding behavior through modulation of reward pathways and alteration of mood. Indeed, certain bacterial species may interact with host metabolism through stimulation of systems outside of the gastrointestinal tract such as the endocannabinoid system impacting gut barrier function and host metabolism [55] as well as the homeostatic and hedonic elements of appetite and food intake [56]. Brain reward signaling is mediated by the dopaminergic mesolimbic system and it has been postulated to play a major role in the development of obesity (for review see [57]). Recently, a human imaging study has shown that increased colonic propionate, one of the main SCFAs secreted by gut bacteria, reduces anticipatory reward responses to high-energy foods via striatal pathways [58]. Gut bacteria may also have impact on this reward system by modulation of gut hormones secretion [58].

It is becoming clear that gut microbiota influences mood and behavior via different mechanisms such as vagus nerve, immune activation, and production of microbial metabolites [4]. Depression and anxiety-like behaviors significantly impact food intake and different associations have been shown between obesity and affective psychiatric disorders (for review see [57]. Increases in psychological stress augments the risk of developing anxiety and depression and activates the hedonic signaling pathway stimulating intake of caloric dense ‘comfort’ foods (for review see [57]. Interestingly, faecal microbiota transplantation from either anxious/obese mice or depressed individuals produces an anxious phenotype while a transplanted into another rodent [59-61]. Moreover, germ-free mice show an exaggerated response to stress [62] and alterations in neurodevelopment and behavior (for review see [63]). More recently, modification of the gut microbiota via prebiotic administration has been shown to have anxiolytic and antidepressant-like effects [64]. The vagus nerve is a key intersection between mood and feeding and has been shown to play a key role in both the behavioural effects of bacteria [65] and feeding behaviours (for review see [42]). Together, it is clear that the gut microbiota may influence mood and eventually affect brain circuits relevant to feeding behaviors.

4. Diet as modifiable factor of microbiota in obesity

The composition of the intestinal microbiota and its function are shaped by both the host's genetic background and external factors, including mode of delivery, environmental elements, exercise as well as nutritional and dietary factors [66]. Most notably, the key determinant affecting gut microbiota composition and activity is diet, whose changes could explain 57% of the total gut microbiota structural variations [67]. Indeed, different dietary components have been show to directly shape the gut microbiota (for review see [14]). Long-term dietary habits have been demonstrated to have profound effects on intestinal microbiota composition in humans [68]. It has been postulated that western diets, in particular, those associated with low microbiota-accessible carbohydrates, found in dietary fiber, have driven the reduced microbiota diversity over generations, compared to populations living in more traditional lifestyles [69].

Interestingly, diet-induced obesity (DIO) in mice following a high fat/high sugar western style diet was associated with an increase in certain Firmicutes, which may be explained by their competitive advantage on processing simple sugars, and a significantly lower abundance of Bacteroidetes [70]. Interestingly, the changes in microbiota were diminished by subsequent dietary manipulations that limit weight gain and adiposity, reinforcing the interaction between diet and distal gut microbiota composition in relation to metabolic function. Microbiota composition also changes significantly with age, from early life colonization to ageing-mediated decline in gut microbial diversity and composition. An altered gut microbiota in older individuals is of particular relevance for health in ageing as the microbiota may modulate aging-related changes in innate immunity, sarcopenia, and cognitive function, all of which are elements of frailty [71]. Moreover, these factors are modified by diet with decreased diversity correlated with increased frailty and markers of inflammation [72].

In addition, recently it has been shown that the microbiome contributes to the accelerated post-dieting weight regain [73]. In this study, an intestinal microbiome signature that persists after successful dieting of obese mice that also contributed to diminished post-dieting flavonoid levels and reduced energy expenditure demonstrating that flavonoid based 'post-biotic' intervention ameliorates excessive secondary weight gain regain. The recognition that diet is a key determinant in short and long term intestinal microbiota composition, diversity and dynamics and subsequent microbiota-driven host metabolic functioning, has generated increasing interest in the potential of designing dietary approaches to enhance the growth of specific beneficial anti-obesity gut microbiota. **Table 1** shows the effects of different components of the diet on the gut microbiota and host metabolism. Fiber is one of the main dietary components affecting the gut microbiota and consist of indigestible carbohydrates which are fermented by bacteria in the gut, leading to the secretion of different beneficial metabolites (e.g. SCFAs) [74]. High-fiber diets have been associated with different positive metabolic effects and a diverse healthy microbiota (for review see [14]). Dietary fat may also indirectly modulate the gut microbiota by its impact on bile acids secretion and composition (for review see [75]). Bile acids have shown selective antimicrobial activity and may therefore mediate the fat-induced effects on the gut microbiota (for review see [75]). In fact, reduced bile salt levels have been associated with bacterial overgrowth in the gut, particularly gram-negative members including LPS producers and pathogens leading to increased inflammation, while increased bile salts levels appear to promote gram-positive members such as *Firmicutes* (for review see [28]). The type of fat influences its effect on health, thus, while saturated fat are not beneficial, unsaturated fat have shown different anti-obesity effects (**Table 1**) [76]. Polyphenols are also gaining prominence as positive modulators of the gut microbiota conferring different beneficial anti-obesity effects

(**Table 1**) [77]. These bioactive dietary compounds have shown different beneficial effects on metabolic syndrome such as reduction of body mass index and waist circumference and improved lipid metabolism as well as reduction of blood pressure and blood glucose (for review see [78]). However, only 5-10% of dietary polyphenols are absorbed in the small intestine while the remaining is accumulated in the large intestine where they interact with the gut microbiota acting as energy substrate for certain beneficial bacteria while inhibiting the growth of pathogenic bacteria (for review see [79]). Thus, due to their low bioavailability it is believed that this prebiotic effect on the gut microbiota is crucial for polyphenol-mediated health effects e.g. [73] (for review see [79]). Dietary proteins are essential nutrients and important part of a balanced diet. They serve as the major source of nitrogen essential for the fermentation of carbohydrates and production of beneficial products such as the SCFAs (for review see [80]). However, the impact of dietary proteins on the gut microbiota remains to be investigated although it seems clear that a high protein diet leads to weight loss but also confides detrimental health effects on the host such as increased risk of colonic diseases, especially when low dietary fiber content diet (**Table 1**). Animal-based diets, which contain higher protein levels compared to plant-based diets, have been shown to increase the abundance of bile-tolerant microorganisms (Alistipes, Bilophila and Bacteroides) and to decrease the levels of Firmicutes that metabolize dietary plant polysaccharides (*Roseburia*, *Eubacterium rectale* and *Ruminococcus bromii*) [81]. Overall, a high fiber low saturated fat diet leads to beneficial anti-obesity effects (**Table 1**). However, the precise mechanisms by which nutritional factors and dietary-strategies modulate intestinal microbial communities and impact on host metabolic signaling needs to be further investigated.

In addition to these dietary components, the gut microbiota composition may be also altered by a variety of others factors such as the use of antibiotics, some components of processed food, sweeteners, stress and even the mode of delivery (**Box 2**). These factors affect the intestinal microbiota in a negative manner causing dysbiosis and, ultimately, affecting the host physiology and metabolism.

Table 1. Effects of different components of the diet on the gut microbiota and host metabolism

Dietary component	Gut microbiota interactions	Gut microbiota changes	Health Effects	References
Fiber/Carbohydrates	Principal carbon and energy source for colonic microbes that are fermented to beneficial metabolites such as SCFA	↑ Bifidobacterium Bacteroidetes *Akkermansia muciniphila* Clostridium Prevotella	Enhanced intestinal barrier integrity Enhanced insulin sensitivity Decreased inflammation Improved lipid metabolism Enhanced intestinal motility Increased satiety	[68] [74] [82] [14] [83]
Proteins	Major source of nitrogen for the gut microbiota, being essential for their assimilation of carbohydrates, but also gases and putrefactive fermentation products	↑ Bacteroidetes ↓ Bifidobacterium	Weight loss Increased risk of atherosclerosis Increased risk of colonic diseases	[84] [14]
Fat	Indirect interaction with the gut microbiota by its impact on bile acids secretion and composition	*Saturated fats*: ↑ Firmicutes Proteobacteria Bilophila ↓ Bacteroidetes Bifidobacterium *Unsaturated fat*: ↑ *Bifidobacterium* *Lactobacillus* *Akkermansia muciniphla*	Increased endotoxemia Reduced insulin sensitivity Increased body weight and adiposity Decreased inflammation and adiposity	[70] [17] [83] [84] [76] [14]
Polyphenols	Energy substrate for certain beneficial bacteria while inhibiting the growth of pathogenic bacteria	↑ Bacteroides Lactobacillus Bifidobacterium *Akkermansia muciniphila* ↓ Clostridium species	reduction of body mass index and waist circumference improved lipid metabolism reduction of blood pressure and blood glucose	[78] [79] [77]

Box. 2 Negative modulators of the Gut microbiota

Antibiotics. Overuse of antibiotics, maternal exposure or via the food chain especially during early-life can have a large impact on the gut microbiota with significant disturbances of its composition and functionality, which can subsequently disrupt gut barrier function and lead to influx of bacterial fragments into the circulation. The resulting low-grade chronic inflammation and metabolic endotoxemia can significantly affect host metabolism and insulin resistance. This microbiota alteration in early-life have long-lasting effects on body weight in adulthood. Indeed, different epidemiological studies have shown that exposure to antibiotics early in life is associated with increased risk of obesity and others related metabolic disorders later in life. For review see [85].

Emulsifiers. These components of processed foods are used to improve food texture and to extend shelf life of food products. A recent study has shown that these dietary emulsifiers impact the gut microbiota promoting colitis and metabolic syndrome in mice. Emulsifier-induced metabolic syndrome was associated with microbiota alterations and increased pro-inflammatory potential. Alterations in gut microbiota composition included reduction in microbial diversity, reduced levels of Bacteroidales, increased levels of several mucolytic bacteria including *Ruminococcus gnavus*, bloom in Verrumicrobia (especially in *Akkermansia muciniphila*) and enriched Proteobacteria. These changes were sufficient for both low-grade inflammation and metabolic syndrome development as demonstrated by use of germ-free mice and faecal transplants [86].

Sweeteners. Non-caloric artificial sweeteners (NAS) are among the most widely used food additives worldwide. Although its consumption has been considered safe and beneficial due to their low caloric content, it has recently been demonstrated that NAS consumption leads to the development of glucose intolerance through compositional and functional alterations in the intestinal microbiota. These alterations included increased abundance of Bacteroides genus and decreased of *Lactobacillus reuteri*. NAS-mediated metabolic effects were prevented by antibiotic treatment, and were transferrable to germ-free mice upon faecal transplantation from NAS-consuming mice, or from microbiota anaerobically incubated in the presence of NAS. Similar NAS-induced dysbiosis and glucose intolerance were also demonstrated in healthy human subjects [87].

C-section. Mode of delivery have also been shown to be crucial for the development of a healthy microbiota. Thus, Dominguez-Bello and colleagues nicely demonstrated that delivery mode shapes the acquisition and structure of the initial microbiota in newborns. Hence, babies born by C-section have a microbiota composition more similar to their mother's skim, dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* spp, while vaginally delivered infants acquired bacterial communities more similar to their mother's vaginal microbiota, dominated by *Lactobacillus*, *Prevotella*, or *Sneathia spp*. These alterations in the gut microbiota composition at early life may impact the host physiology and metabolism later in life. Indeed, different epidemiological studies have reported associations between C-section delivery and an increased risk of obesity, asthma, allergies and immune deficiencies [88].

Stress. The hypothalamus–pituitary–adrenal (HPA) axis activity associated to stress have been shown to influence the composition of the gut microbiota. Thus, early exposure to stress leads to a decreased gut microbiota diversity and may have long-term effects on its composition. Moreover, chronic stress in adulthood also have an impact on the intestinal microbiota composition with a decrease in *Bacteroides* and *Clostridium* spp., and it also lead to increased inflammation, which is indicative of immune activation. Furthermore, chronic stress also alters the intestinal barrier integrity increasing the circulating levels of immunomodulatory bacterial cell wall components such as lipopolysaccharide. For review see [89].

5. Towards Therapeutic Strategies

Considering the key role of the gut microbiota in regulation of the host's metabolism, energy homeostasis and central appetite regulation, it is not surprising that the microbiota is now a target to combat metabolic disorders such as obesity. Indeed, gut microbiota-based treatment strategies have subsequent effects on host's metabolism. However, subsequent advances in the field are needed before they can be used as therapeutic tools to curb appetite and food intake and restore metabolic imbalances in disorders such as obesity.

5.1 Probiotics as anti-obesity treatments

Western diet is driving us towards obesity development via different mechanisms in which specific gut microbiota changes play a key role. Hence, western diet as well as the use of preservatives and emulsifiers in the food industry is leading to the increased Firmicutes/Bacteroidetes ratio characteristic in obese individuals[70, 86]. Thus, strategies to reverse this obesity-induced changes in microbiota composition are of crucial pharmacological and nutritional interest in the management of obesity and obesity-related disorders. Dietary interventions by probiotic administration may be one of the approaches to modulate and maintain a healthy microbiota composition. Probiotics are defined as "live microorganisms that, when administrated in adequate amounts, confer beneficial health effects on the host" (for review see [89]). Recent studies have highlighted the potential role of probiotics in the treatment of obesity. Hence, different bacterial strains have shown beneficial anti-obesity effects such as reduction of tissue inflammation, endotoxemia, adiposity, body weight, leptin levels and energy intake (for review see [44]). However, most of these studies have been carried out in rodent models and, therefore, more human studies are needed to support the potential of these probiotic strains as alternative to treat and/or prevent obesity. The most common probiotic species that have shown these anti-obesity effects are *Bifidobacterium* and *Lactobacillus* species. More recently, *Akkermansia muciniphila* has emerged as one of the main gut bacteria influencing host metabolism with the capability to reverse high-fat diet-induced metabolic effects such as fat-mass gain, metabolic endotoxemia, adipose tissue inflammation, and insulin resistance [90]. All these beneficial bacteria interact with different components of the diet, mainly with insoluble fiber, releasing different bioactive metabolites that signal to the host via different mechanisms involved in the gut-brain axis (for review see [83]). Further studies are poised in order to elucidate the mechanism by which specific probiotics can harvest energy from food and nutrients.

5.2 Prebiotics as dietary intervention in obesity

In addition to the direct administration of live bacteria in the form of probiotics, the growth promotion in the gut of specific beneficial bacteria over other unfavorable commensal species may be achieved by administration of prebiotics. These have been recently re-defined as "non-digestible compounds that, through its metabolization by microorganisms in the gut, modulates composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect on the host" [82]. Although dietary carbohydrates, such as oligosaccharides like insulin, fructo-oligosaccharides, and galacto-oligosaccharides, are the most widely used prebiotics, other compounds, such as polyphenols may also fit in this definition (for review see [82]). Administration of fiber-rich diets have been shown to increase the abundance of different beneficial bacteria in the gut, such as *Bifidobacterium* and *Lactobacillus* species, leading to different anti-obesity effects including reduction of endotoxemia and enhanced intestinal barrier function through increased expression of tight junction proteins and decreased circulating pro-inflammatory cytokines (for review see [44]). Indeed, a lower number of these bacterial species has been related to obesity and type 2 diabetes compared to healthy individuals (for review see [44]). However, most of the studies are based on correlations rather than in a causal link between the modulation of the gut microbiota and the observed beneficial metabolic and physiological effects. Therefore, more studies are needed to elucidate the potential mechanisms involved on the prebiotics-mediated beneficial effects (for review see [82]).

5.3 Faecal Microbiota Transplant (FMT)

A promising new strategy to alter the gut microbiota composition is by FMT from healthy donors into the patient's intestinal tract, typically by colonoscopy or duodenal endoscopy, resulting in the restoration of normal gut microbial community structure and functionality [91]. Indeed, it has been recently found in humans that donor microbial strains can colonize the recipient gut microbiota and persist for at least three months after FMT [92]. However, donor–recipient compatibilities are important for a successful establishment of the donor's strains in the new recipient environment, with a higher possibility to prosper if the species were already present in the recipient [92].

FMT has successfully been used to treat *Clostridium difficile* infections (CDI) with more than 90% of efficacy (for review see [93]). This high efficacy rate is a hopeful indication of the power of FMT to modify the gut microbiota and, therefore, of its potential as therapeutic for others diseases where gut microbiota dysbiosis is also involved, such as ulcerative colitis (UC), irritable bowel syndrome (IBS), chronic constipation and Crohn's disease (CD). However, no conclusive results have been shown so far in this regard and more studies need to be done in order to draw conclusions about the efficacy of FMT as a therapeutic option for these gastrointestinal disorders [91]. In addition, there is increasing evidences that FMT may also have potential in the treatment of obesity and related disorders such as type 2 diabetes. Interestingly, transfer of gut microbiota through a duodenal tube from healthy, lean donors to obese individuals diagnosed with T2D have been shown to increase insulin sensitivity along with increased faecal microbiota diversity and butyrate-producing intestinal bacteria from the Clostridium cluster XIVa as well as with decreased fecal SCFA [94]. Moreover, a case study reported how a woman successfully treated with FMT developed new-onset obesity after receiving stool from a healthy but overweight donor [95]. This is however controversial, as it is only a case report so far. Nevertheless, these findings are consistent with others observations in animal models, and previously discussed in this review, where the obesity phenotype was transferred to germ-free mice by FMT from obese donors [19]. FMT may also have some potential risks such as the spread of transmissible disease. However, no such as side effects have been reported but only mild effects including diarrhea or fever (for review see [96]).

6. Conclusion and outlook

Host microbe interactions are key for optimal health. Commensal bacteria exert a plethora of structural and protective effects on the intestinal mucosa, but also influence metabolic aspects of the host. Accumulating evidence from both human and rodent studies is highlighting the central role of the gut microbiota on the gut-brain axis and its implication on central appetite modulation. Moreover, the link between intestinal microbiota composition and metabolic dysfunction or obesity is becoming clear and has been extensively reported. Therefore, modulation of the gut microbiota may have great potential as therapeutic for the treatment of obesity and other metabolic diseases such as diabetes. While pre- and probiotics are one of the most widely used strategies to modulate the gut microbiota and hence improve metabolic imbalances, other strategies that modify the gut microbiota, including other dietary components such as polyphenols as well as interventions such as bariatric surgery and FMT, should also be considered.

References

1. Ottman, N., H. Smidt, W.M. de Vos, and C. Belzer, *The function of our microbiota: who is out there and what do they do?* Front Cell Infect Microbiol, 2012. 2: p. 104.
2. Eckburg, P.B., E.M. Bik, C.N. Bernstein, E. Purdom, L. Dethlefsen, M. Sargent, S.R. Gill, K.E. Nelson, and D.A. Relman, *Diversity of the human intestinal microbial flora.* Science, 2005. 308(5728): p. 1635-8.
3. Patterson, E., P.M. Ryan, J.F. Cryan, T.G. Dinan, R.P. Ross, G.F. Fitzgerald, and C. Stanton, *Gut microbiota, obesity and diabetes.* Postgrad Med J, 2016. 92(1087): p. 286-300.
4. Dinan, T.G. and J.F. Cryan, *Mood by microbe: towards clinical translation.* Genome Med, 2016. 8(1): p. 36.
5. Neufeld, K.A., N. Kang, J. Bienenstock, and J.A. Foster, *Effects of intestinal microbiota on anxiety-like behavior.* Commun Integr Biol, 2011. 4(4): p. 492-4.
6. Backhed, F., H. Ding, T. Wang, L.V. Hooper, G.Y. Koh, A. Nagy, C.F. Semenkovich, and J.I. Gordon, *The gut microbiota as an environmental factor that regulates fat storage.* Proc Natl Acad Sci U S A, 2004. 101(44): p. 15718-23.
7. Turnbaugh, P.J., R.E. Ley, M.A. Mahowald, V. Magrini, E.R. Mardis, and J.I. Gordon, *An obesity-associated gut microbiome with increased capacity for energy harvest.* Nature, 2006. 444(7122): p. 1027-31.
8. Khan, M.J., K. Gerasimidis, C.A. Edwards, and M.G. Shaikh, *Role of Gut Microbiota in the Aetiology of Obesity: Proposed Mechanisms and Review of the Literature.* J Obes, 2016. 2016: p. 7353642.
9. Fetissov, S.O., *Role of the gut microbiota in host appetite control: bacterial growth to animal feeding behaviour.* Nat Rev Endocrinol, 2016.
10. Cox, L.M., S. Yamanishi, J. Sohn, A.V. Alekseyenko, J.M. Leung, I. Cho, S.G. Kim, H. Li, Z. Gao, D. Mahana, J.G. Zarate Rodriguez, A.B. Rogers, N. Robine, P. Loke, and M.J. Blaser, *Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences.* Cell, 2014. 158(4): p. 705-21.
11. Aron-Wisnewsky, J. and K. Clement, *The effects of gastrointestinal surgery on gut microbiota: potential contribution to improved insulin sensitivity.* Curr Atheroscler Rep, 2014. 16(11): p. 454.
12. Bloom, S.R., F.P. Kuhajda, I. Laher, X. Pi-Sunyer, G.V. Ronnett, T.M. Tan, and D.S. Weigle, *The obesity epidemic: pharmacological challenges.* Mol Interv, 2008. 8(2): p. 82-98.
13. O'Neill, S. and L. O'Driscoll, *Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies.* Obes Rev, 2015. 16(1): p. 1-12.
14. Sandhu, K.V., E. Sherwin, H. Schellekens, C. Stanton, T.G. Dinan, and J.F. Cryan, *Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry.* Transl Res, 2016.
15. Duca, F.A., T.D. Swartz, Y. Sakar, and M. Covasa, *Increased oral detection, but decreased intestinal signaling for fats in mice lacking gut microbiota.* PLoS One, 2012. 7(6): p. e39748.
16. Ley, R.E., F. Backhed, P. Turnbaugh, C.A. Lozupone, R.D. Knight, and J.I. Gordon, *Obesity alters gut microbial ecology.* Proc Natl Acad Sci U S A, 2005. 102(31): p. 11070-11075.
17. Turnbaugh, P.J. and J.I. Gordon, *The core gut microbiome, energy balance and obesity.* J Physiol, 2009. 587(Pt 17): p. 4153-8.
18. Turnbaugh, P.J., R.E. Ley, M.A. Mahowald, V. Magrini, E.R. Mardis, and J.I. Gordon, *An obesity-associated gut microbiome with increased capacity for energy harvest.* Nature, 2006. 444(7122): p. 1027-1031.
19. Ridaura, V.K., J.J. Faith, F.E. Rey, J. Cheng, A.E. Duncan, A.L. Kau, N.W. Griffin, V. Lombard, B. Henrissat, J.R. Bain, M.J. Muehlbauer, O. Ilkayeva, C.F. Semenkovich, K. Funai, D.K. Hayashi, B.J. Lyle, M.C. Martini, L.K. Ursell, J.C. Clemente, W. Van Treuren, W.A. Walters, R. Knight, C.B.

Newgard, A.C. Heath, and J.I. Gordon, *Gut microbiota from twins discordant for obesity modulate metabolism in mice.* Science, 2013. 341(6150): p. 1241214.

20. Sze, M.A. and P.D. Schloss, *Looking for a Signal in the Noise: Revisiting Obesity and the Microbiome.* MBio, 2016. 7(4).
21. Ussar, S., N.W. Griffin, O. Bezy, S. Fujisaka, S. Vienberg, S. Softic, L. Deng, L. Bry, J.I. Gordon, and C.R. Kahn, *Interactions between Gut Microbiota, Host Genetics and Diet Modulate the Predisposition to Obesity and Metabolic Syndrome.* Cell Metab, 2015. 22(3): p. 516-30.
22. Goodrich, J.K., J.L. Waters, A.C. Poole, J.L. Sutter, O. Koren, R. Blekhman, M. Beaumont, W. Van Treuren, R. Knight, J.T. Bell, T.D. Spector, A.G. Clark, and R.E. Ley, *Human genetics shape the gut microbiome.* Cell, 2014. 159(4): p. 789-99.
23. Zhang, L.S. and S.S. Davies, *Microbial metabolism of dietary components to bioactive metabolites: opportunities for new therapeutic interventions.* Genome Med, 2016. 8(1): p. 46.
24. Krajmalnik-Brown, R., Z.E. Ilhan, D.W. Kang, and J.K. DiBaise, *Effects of gut microbes on nutrient absorption and energy regulation.* Nutr Clin Pract, 2012. 27(2): p. 201-14.
25. Murphy, E.F., P.D. Cotter, S. Healy, T.M. Marques, O. O'Sullivan, F. Fouhy, S.F. Clarke, P.W. O'Toole, E.M. Quigley, C. Stanton, P.R. Ross, R.M. O'Doherty, and F. Shanahan, *Composition and energy harvesting capacity of the gut microbiota: relationship to diet, obesity and time in mouse models.* Gut, 2010. 59(12): p. 1635-42.
26. Boulange, C.L., A.L. Neves, J. Chilloux, J.K. Nicholson, and M.E. Dumas, *Impact of the gut microbiota on inflammation, obesity, and metabolic disease.* Genome Med, 2016. 8(1): p. 42.
27. Bäckhed, F., J. Manchester, C. Semenkovich, and J. Gordon, *Mechanisms underlying the resistance to diet-induced obesity in germ-free mice.* Proc Natl Acad Sci U S A, 2007. 104(3): p. 979-984.
28. Ridlon, J.M., D.J. Kang, P.B. Hylemon, and J.S. Bajaj, *Bile acids and the gut microbiome.* Curr Opin Gastroenterol, 2014. 30(3): p. 332-8.
29. Cani, P.D., A. Everard, and T. Duparc, *Gut microbiota, enteroendocrine functions and metabolism.* Curr Opin Pharmacol, 2013. 13(6): p. 935-40.
30. Thomas, C., A. Gioiello, L. Noriega, A. Strehle, J. Oury, G. Rizzo, A. Macchiarulo, H. Yamamoto, C. Mataki, M. Pruzanski, R. Pellicciari, J. Auwerx, and K. Schoonjans, *TGR5-mediated bile acid sensing controls glucose homeostasis.* Cell Metab, 2009. 10(3): p. 167-77.
31. Zhang, Y., X. Ge, L.A. Heemstra, W.D. Chen, J. Xu, J.L. Smith, H. Ma, N. Kasim, P.A. Edwards, and C.M. Novak, *Loss of FXR protects against diet-induced obesity and accelerates liver carcinogenesis in ob/ob mice.* Mol Endocrinol, 2012. 26(2): p. 272-80.
32. Trabelsi, M.S., S. Lestavel, B. Staels, and X. Collet, *Intestinal bile acid receptors are key regulators of glucose homeostasis.* Proc Nutr Soc, 2016: p. 1-11.
33. Staels, B. and V.A. Fonseca, *Bile acids and metabolic regulation: mechanisms and clinical responses to bile acid sequestration.* Diabetes Care, 2009. 32 Suppl 2: p. S237-45.
34. O'Mahony, S.M., G. Clarke, Y.E. Borre, T.G. Dinan, and J.F. Cryan, *Serotonin, tryptophan metabolism and the brain-gut-microbiome axis.* Behav Brain Res, 2015. 277: p. 32-48.
35. Nonogaki, K. and T. Kaji, *Pharmacological stimulation of serotonin 5-HT1B receptors enhances increases in plasma active glucagon-like peptide-1 levels induced by dipeptidyl peptidase-4 inhibition independently of feeding in mice.* Diabetes Metab, 2015. 41(5): p. 425-8.
36. Dumas, M.E., R.H. Barton, A. Toye, O. Cloarec, C. Blancher, A. Rothwell, J. Fearnside, R. Tatoud, V. Blanc, J.C. Lindon, S.C. Mitchell, E. Holmes, M.I. McCarthy, J. Scott, D. Gauguier, and J.K. Nicholson, *Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice.* Proc Natl Acad Sci U S A, 2006. 103(33): p. 12511-6.
37. Parseus, A., N. Sommer, F. Sommer, R. Caesar, A. Molinaro, M. Stahlman, T.U. Greiner, R. Perkins, and F. Backhed, *Microbiota-induced obesity requires farnesoid X receptor.* Gut, 2016.

38. Delzenne, N.M., A.M. Neyrinck, F. Backhed, and P.D. Cani, *Targeting gut microbiota in obesity: effects of prebiotics and probiotics.* Nat Rev Endocrinol, 2011. 7(11): p. 639-46.
39. Rooks, M.G. and W.S. Garrett, *Gut microbiota, metabolites and host immunity.* Nat Rev Immunol, 2016. 16(6): p. 341-52.
40. Schellekens, H., T.G. Dinan, and J.F. Cryan, *Lean mean fat reducing "ghrelin" machine: hypothalamic ghrelin and ghrelin receptors as therapeutic targets in obesity.* Neuropharmacology, 2010. 58(1): p. 2-16.
41. Abbott, C.R., M. Monteiro, C.J. Small, A. Sajedi, K.L. Smith, J.R. Parkinson, M.A. Ghatei, and S.R. Bloom, *The inhibitory effects of peripheral administration of peptide YY(3-36) and glucagon-like peptide-1 on food intake are attenuated by ablation of the vagal-brainstem-hypothalamic pathway.* Brain Res, 2005. 1044(1): p. 127-31.
42. Bodenlos, J.S., K.L. Schneider, J. Oleski, K. Gordon, A.J. Rothschild, and S.L. Pagoto, *Vagus nerve stimulation and food intake: effect of body mass index.* J Diabetes Sci Technol, 2014. 8(3): p. 590-5.
43. Everard, A. and P.D. Cani, *Gut microbiota and GLP-1.* Rev Endocr Metab Disord, 2014. 15(3): p. 189-96.
44. Torres-Fuentes, C., H. Schellekens, T.G. Dinan, and J.F. Cryan, *A natural solution for obesity: Bioactives for the prevention and treatment of weight gain. A review.* Nutr Neurosci, 2014.
45. Nohr, M.K., M.H. Pedersen, A. Gille, K.L. Egerod, M.S. Engelstoft, A.S. Husted, R.M. Sichlau, K.V. Grunddal, S.S. Poulsen, S. Han, R.M. Jones, S. Offermanns, and T.W. Schwartz, *GPR41/FFAR3 and GPR43/FFAR2 as cosensors for short-chain fatty acids in enteroendocrine cells vs FFAR3 in enteric neurons and FFAR2 in enteric leukocytes.* Endocrinology, 2013. 154(10): p. 3552-64.
46. Frost, G., M.L. Sleeth, M. Sahuri-Arisoylu, B. Lizarbe, S. Cerdan, L. Brody, J. Anastasovska, S. Ghourab, M. Hankir, S. Zhang, D. Carling, J.R. Swann, G. Gibson, A. Viardot, D. Morrison, E. Louise Thomas, and J.D. Bell, *The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism.* Nat Commun, 2014. 5: p. 3611.
47. Perry, R.J., L. Peng, N.A. Barry, G.W. Cline, D. Zhang, R.L. Cardone, K.F. Petersen, R.G. Kibbey, A.L. Goodman, and G.I. Shulman, *Acetate mediates a microbiome-brain-beta-cell axis to promote metabolic syndrome.* Nature, 2016. 534(7606): p. 213-7.
48. Calvo, S.S. and J.M. Egan, *The endocrinology of taste receptors.* Nat Rev Endocrinol, 2015. 11(4): p. 213-27.
49. Swartz, T.D., F.A. Duca, T. de Wouters, Y. Sakar, and M. Covasa, *Up-regulation of intestinal type 1 taste receptor 3 and sodium glucose luminal transporter-1 expression and increased sucrose intake in mice lacking gut microbiota.* Br J Nutr, 2012. 107(5): p. 621-30.
50. Wall, R., J.F. Cryan, R.P. Ross, G.F. Fitzgerald, T.G. Dinan, and C. Stanton, *Bacterial neuroactive compounds produced by psychobiotics.* Adv Exp Med Biol, 2014. 817: p. 221-39.
51. Meng, F., Y. Han, D. Srisai, V. Belakhov, M. Farias, Y. Xu, R.D. Palmiter, T. Baasov, and Q. Wu, *New inducible genetic method reveals critical roles of GABA in the control of feeding and metabolism.* Proc Natl Acad Sci U S A, 2016. 113(13): p. 3645-50.
52. Delgado, T.C., *Glutamate and GABA in Appetite Regulation.* Front Endocrinol (Lausanne), 2013. 4: p. 103.
53. Heisler, L.K., E.E. Jobst, G.M. Sutton, L. Zhou, E. Borok, Z. Thornton-Jones, H.Y. Liu, J.M. Zigman, N. Balthasar, T. Kishi, C.E. Lee, C.J. Aschkenasi, C.Y. Zhang, J. Yu, O. Boss, K.G. Mountjoy, P.G. Clifton, B.B. Lowell, J.M. Friedman, T. Horvath, A.A. Butler, J.K. Elmquist, and M.A. Cowley, *Serotonin reciprocally regulates melanocortin neurons to modulate food intake.* Neuron, 2006. 51(2): p. 239-49.

54. Xu, Y., J.E. Jones, D. Kohno, K.W. Williams, C.E. Lee, M.J. Choi, J.G. Anderson, L.K. Heisler, J.M. Zigman, B.B. Lowell, and J.K. Elmquist, *5-HT2CRs expressed by pro-opiomelanocortin neurons regulate energy homeostasis.* Neuron, 2008. 60(4): p. 582-9.
55. Cani, P.D., H. Plovier, M. Van Hul, L. Geurts, N.M. Delzenne, C. Druart, and A. Everard, *Endocannabinoids--at the crossroads between the gut microbiota and host metabolism.* Nat Rev Endocrinol, 2016. 12(3): p. 133-43.
56. Jager, G. and R.F. Witkamp, *The endocannabinoid system and appetite: relevance for food reward.* Nutr Res Rev, 2014. 27(1): p. 172-85.
57. Schellekens, H., B.C. Finger, T.G. Dinan, and J.F. Cryan, *Ghrelin signalling and obesity: at the interface of stress, mood and food reward.* Pharmacol Ther, 2012. 135(3): p. 316-26.
58. Byrne, C.S., E.S. Chambers, H. Alhabeeb, N. Chhina, D.J. Morrison, T. Preston, C. Tedford, J. Fitzpatrick, C. Irani, A. Busza, I. Garcia-Perez, S. Fountana, E. Holmes, A.P. Goldstone, and G.S. Frost, *Increased colonic propionate reduces anticipatory reward responses in the human striatum to high-energy foods.* Am J Clin Nutr, 2016. 104(1): p. 5-14.
59. Collins, S.M., Z. Kassam, and P. Bercik, *The adoptive transfer of behavioral phenotype via the intestinal microbiota: experimental evidence and clinical implications.* Curr Opin Microbiol, 2013. 16(3): p. 240-5.
60. Kelly, J.R., Y. Borre, O.B. C, E. Patterson, S. El Aidy, J. Deane, P.J. Kennedy, S. Beers, K. Scott, G. Moloney, A.E. Hoban, L. Scott, P. Fitzgerald, P. Ross, C. Stanton, G. Clarke, J.F. Cryan, and T.G. Dinan, *Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat.* J Psychiatr Res, 2016. 82: p. 109-18.
61. Bruce-Keller, A.J., J.M. Salbaum, M. Luo, E.t. Blanchard, C.M. Taylor, D.A. Welsh, and H.R. Berthoud, *Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity.* Biol Psychiatry, 2015. 77(7): p. 607-15.
62. Sudo, N., Y. Chida, Y. Aiba, J. Sonoda, N. Oyama, X.N. Yu, C. Kubo, and Y. Koga, *Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice.* J Physiol, 2004. 558(Pt 1): p. 263-75.
63. Dinan, T.G. and J.F. Cryan, *Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration.* J Physiol, 2017. 595(2): p. 489-503.
64. Burokas, A.e.a., *Targeting the Microbiota-Gut-Brain Axis: Prebiotics Have Anxiolytic and Antidepressant-like Effects and Reverse the Impact of Chronic Stress in Mice* Biological Psychiatry In Press, 2017.
65. Bravo, J.A., P. Forsythe, M.V. Chew, E. Escaravage, H.M. Savignac, T.G. Dinan, J. Bienenstock, and J.F. Cryan, *Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve.* Proc Natl Acad Sci U S A, 2011. 108(38): p. 16050-5.
66. Borre, Y.E., G.W. O'Keeffe, G. Clarke, C. Stanton, T.G. Dinan, and J.F. Cryan, *Microbiota and neurodevelopmental windows: implications for brain disorders.* Trends Mol Med, 2014. 20(9): p. 509-18.
67. Zhang, C., M. Zhang, S. Wang, R. Han, Y. Cao, W. Hua, Y. Mao, X. Zhang, X. Pang, C. Wei, G. Zhao, Y. Chen, and L. Zhao, *Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice.* ISME J, 2010. 4(2): p. 232-41.
68. De Filippo, C., D. Cavalieri, M. Di Paola, M. Ramazzotti, J.B. Poullet, S. Massart, S. Collini, G. Pieraccini, and P. Lionetti, *Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa.* Proc Natl Acad Sci U S A, 2010. 107(33): p. 14691-6.

69. Sonnenburg, E.D., S.A. Smits, M. Tikhonov, S.K. Higginbottom, N.S. Wingreen, and J.L. Sonnenburg, *Diet-induced extinctions in the gut microbiota compound over generations.* Nature, 2016. 529(7585): p. 212-5.
70. Turnbaugh, P., F. Bäckhed, L. Fulton, and J. Gordon, *Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome.* Cell Host Microbe, 2008. 3(4): p. 213-223.
71. O'Toole, P.W. and I.B. Jeffery, *Gut microbiota and aging.* Science, 2015. 350(6265): p. 1214-5.
72. Claesson, M.J., I.B. Jeffery, S. Conde, S.E. Power, E.M. O'Connor, S. Cusack, H.M. Harris, M. Coakley, B. Lakshminarayanan, O. O'Sullivan, G.F. Fitzgerald, J. Deane, M. O'Connor, N. Harnedy, K. O'Connor, D. O'Mahony, D. van Sinderen, M. Wallace, L. Brennan, C. Stanton, J.R. Marchesi, A.P. Fitzgerald, F. Shanahan, C. Hill, R.P. Ross, and P.W. O'Toole, *Gut microbiota composition correlates with diet and health in the elderly.* Nature, 2012. 488(7410): p. 178-84.
73. Thaiss, C.A., S. Itav, D. Rothschild, M. Meijer, M. Levy, C. Moresi, L. Dohnalova, S. Braverman, S. Rozin, S. Malitsky, M. Dori-Bachash, Y. Kuperman, I. Biton, A. Gertler, A. Harmelin, H. Shapiro, Z. Halpern, A. Aharoni, E. Segal, and E. Elinav, *Persistent microbiome alterations modulate the rate of post-dieting weight regain.* Nature, 2016.
74. Slavin, J., *Fiber and prebiotics: mechanisms and health benefits.* Nutrients, 2013. 5(4): p. 1417-35.
75. Graf, D., R. Di Cagno, F. Fak, H.J. Flint, M. Nyman, M. Saarela, and B. Watzl, *Contribution of diet to the composition of the human gut microbiota.* Microb Ecol Health Dis, 2015. 26: p. 26164.
76. Caesar, R., V. Tremaroli, P. Kovatcheva-Datchary, P.D. Cani, and F. Backhed, *Crosstalk between Gut Microbiota and Dietary Lipids Aggravates WAT Inflammation through TLR Signaling.* Cell Metab, 2015. 22(4): p. 658-68.
77. Cardona, F., C. Andres-Lacueva, S. Tulipani, F.J. Tinahones, and M.I. Queipo-Ortuno, *Benefits of polyphenols on gut microbiota and implications in human health.* J Nutr Biochem, 2013. 24(8): p. 1415-22.
78. Amiot, M.J., C. Riva, and A. Vinet, *Effects of dietary polyphenols on metabolic syndrome features in humans: a systematic review.* Obes Rev, 2016. 17(7): p. 573-86.
79. Ozdal, T., D.A. Sela, J. Xiao, D. Boyacioglu, F. Chen, and E. Capanoglu, *The Reciprocal Interactions between Polyphenols and Gut Microbiota and Effects on Bioaccessibility.* Nutrients, 2016. 8(2): p. 78.
80. Conlon, L.E., M.A. Wallig, and J.W. Erdman, Jr., *Low-lycopene containing tomato powder diet does not protect against prostate cancer in TRAMP mice.* Nutr Res, 2015. 35(10): p. 882-90.
81. David, L.A., C.F. Maurice, R.N. Carmody, D.B. Gootenberg, J.E. Button, B.E. Wolfe, A.V. Ling, A.S. Devlin, Y. Varma, M.A. Fischbach, S.B. Biddinger, R.J. Dutton, and P.J. Turnbaugh, *Diet rapidly and reproducibly alters the human gut microbiome.* Nature, 2014. 505(7484): p. 559-63.
82. Bindels, L.B., N.M. Delzenne, P.D. Cani, and J. Walter, *Towards a more comprehensive concept for prebiotics.* Nat Rev Gastroenterol Hepatol, 2015. 12(5): p. 303-10.
83. Sonnenburg, J.L. and F. Backhed, *Diet-microbiota interactions as moderators of human metabolism.* Nature, 2016. 535(7610): p. 56-64.
84. Conlon, M.A. and A.R. Bird, *The Impact of Diet and Lifestyle on Gut Microbiota and Human Health.* Nutrients, 2015. 7(1): p. 17-44.
85. Cox, L.M. and M.J. Blaser, *OPINION Antibiotics in early life and obesity.* Nature Reviews Endocrinology, 2015. 11(3): p. 182-190.
86. Chassaing, B., O. Koren, J.K. Goodrich, A.C. Poole, S. Srinivasan, R.E. Ley, and A.T. Gewirtz, *Corrigendum: Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome.* Nature, 2016. 536(7615): p. 238.

87. Suez, J., T. Korem, D. Zeevi, G. Zilberman-Schapira, C.A. Thaiss, O. Maza, D. Israeli, N. Zmora, S. Gilad, A. Weinberger, Y. Kuperman, A. Harmelin, I. Kolodkin-Gal, H. Shapiro, Z. Halpern, E. Segal, and E. Elinav, *Artificial sweeteners induce glucose intolerance by altering the gut microbiota.* Nature, 2014. 514(7521): p. 181-6.
88. Dominguez-Bello, M.G., E.K. Costello, M. Contreras, M. Magris, G. Hidalgo, N. Fierer, and R. Knight, *Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns.* Proc Natl Acad Sci U S A, 2010. 107(26): p. 11971-5.
89. Cryan, J.F. and T.G. Dinan, *Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour.* Nat Rev Neurosci, 2012. 13(10): p. 701-12.
90. Everard, A., C. Belzer, L. Geurts, J.P. Ouwerkerk, C. Druart, L.B. Bindels, Y. Guiot, M. Derrien, G.G. Muccioli, N.M. Delzenne, W.M. de Vos, and P.D. Cani, *Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity.* Proc Natl Acad Sci U S A, 2013. 110(22): p. 9066-71.
91. Khoruts, A. and M.J. Sadowsky, *Understanding the mechanisms of faecal microbiota transplantation.* Nat Rev Gastroenterol Hepatol, 2016. 13(9): p. 508-16.
92. Li, S.S., A. Zhu, V. Benes, P.I. Costea, R. Hercog, F. Hildebrand, J. Huerta-Cepas, M. Nieuwdorp, J. Salojarvi, A.Y. Voigt, G. Zeller, S. Sunagawa, W.M. de Vos, and P. Bork, *Durable coexistence of donor and recipient strains after fecal microbiota transplantation.* Science, 2016. 352(6285): p. 586-9.
93. Li, Y.T., H.F. Cai, Z.H. Wang, J. Xu, and J.Y. Fang, *Systematic review with meta-analysis: long-term outcomes of faecal microbiota transplantation for Clostridium difficile infection.* Aliment Pharmacol Ther, 2016. 43(4): p. 445-57.
94. Vrieze, A., E. Van Nood, F. Holleman, J. Salojarvi, R.S. Kootte, J.F. Bartelsman, G.M. Dallinga-Thie, M.T. Ackermans, M.J. Serlie, R. Oozeer, M. Derrien, A. Druesne, J.E. Van Hylckama Vlieg, V.W. Bloks, A.K. Groen, H.G. Heilig, E.G. Zoetendal, E.S. Stroes, W.M. de Vos, J.B. Hoekstra, and M. Nieuwdorp, *Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome.* Gastroenterology, 2012. 143(4): p. 913-6 e7.
95. Alang, N. and C.R. Kelly, *Weight gain after fecal microbiota transplantation.* Open Forum Infect Dis, 2015. 2(1): p. ofv004.
96. Marotz, C.A. and A. Zarrinpar, *Treating Obesity and Metabolic Syndrome with Fecal Microbiota Transplantation.* Yale J Biol Med, 2016. 89(3): p. 383-388.