doi: 10.1111/obr.12661

Etiology and Pathophysiology

Microbiota in obesity: interactions with enteroendocrine, immune and central nervous systems

R. J. Mulders[1], K. C. G. de Git[2], E. Schéle[3], S. L. Dickson[3], Y. Sanz[4] and R. A. H. Adan[2]

[1]Master's Programme Science and Business Management, Utrecht University, Utrecht, The Netherlands, [2]Department of Translational Neuroscience, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands, [3]Institute for Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden, and [4]Microbial Ecology, Nutrition and Health Research Group, Institute of Agrochemistry and Food Technology, National Research Council (IATA-CSIC), Valencia, Spain

Received 21 September 2017; revised 27 November 2017; accepted 27 November 2017

Address for correspondence: RAH Adan, Department of Translational Neuroscience, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands.
E-mail: r.a.h.adan@umcutrecht.nl

Summary

Western diets, with high consumption of simple sugars and saturated fats, contribute to the rise in the prevalence of obesity. It now seems clear that high-fat diets cause obesity, at least in part, by modifying the composition and function of the microorganisms that colonize in the gastrointestinal tract, the microbiota. The exact pathways by which intestinal microbiota contribute to obesity remain largely unknown. High-fat diet-induced alterations in intestinal microbiota have been suggested to increase energy extraction, intestinal permeability and systemic inflammation while decreasing the capability to generate obesity-suppressing short-chain fatty acids. Moreover, by increasing systemic inflammation, microglial activation and affecting vagal nerve activity, 'obese microbiota' indirectly influence hypothalamic gene expression and promote overeating. Because the potential of intestinal microbiota to induce obesity has been recognized, multiple ways to modify its composition and function are being investigated to provide novel preventive and therapeutic strategies against diet-induced obesity.

Keywords: hypothalamus, inflammation, microbiota, obesity.

Introduction

In recent years, we have seen the emergence of many popular theories that explain the current global pandemic in obesity. Whatever the cause, one fact remains: Major drivers include an increased availability and consumption of energy-dense diets that are high in fat (1–3). To study how high-fat diets (HFD) cause obesity, a number of animal models have been developed (4–7). In such models of diet-induced obesity (DIO), it has been shown that HFD feeding impacts upon hypothalamic pathways, altering expression of genes pivotal for feeding control (8,9). However, the exact mechanisms behind these effects are largely unknown.

One popular theory for DIO, for which there is a considerable evidence base, implicates the composition of intestinal microbiota and its genome (microbiome) which are modifiable by the diet (10–13). Intestinal microbiota is a complex ecosystem mainly composed of bacteria that colonize in the gastrointestinal tract and consist of at least as many bacterial cells as there are cells in the human body (14). Although similar in number, the human microbiota carries at least 150 times more genes than the human genome (15) and provides additional metabolic capabilities that influence human physiology (11). Most of the bacterial species inhabiting the human intestinal tract belong to the phyla Firmicutes (60–80%) and Bacteroidetes (15–25%),

while others, such as those belonging to the phyla Proteobacteria (1–10%), Actinobacteria (2.5–5%) and Verrucomicrobia (0.1–2.2%) (13,16–18), are less abundant. There are indications that properties of the host (such as its genome) determine the type of intestinal microbiota (19), and this also appears to be species-specific (20). However, a proportion of microbial communities can also rapidly respond to environmental factors like diet, thus representing an important source of metabolic flexibility and phenotypic plasticity for the host (21). Consequently, significant differences are found in microbiota of different mouse colonies (22) and human populations (17).

In this review, we focus, in particular, on the effects of HFD on the composition and function of the microbiota. We select HFD rather than diets high in both fat and sugar because the effects of HFD on microbiota are more consistent and better documented in relation to obesity. This is likely because sucrose has an independent, unique effect on the microbiota (23) and also because the interactions between sucrose and HFD on the microbiota are largely unknown, and possibly confusing (24). In line with our previous publication (25), we hypothesize that DIO-induced variations in microbiota composition promote hypothalamic inflammation and alter hypothalamic gene expression to cause central leptin resistance and obesity. Supportively, we hereby provide an extensive overview of the effects of HFD feeding on microbiota and their relationship with host biomarkers with a view to pinpoint potential beneficial and detrimental bacteria for the development of obesity. We also review the currently known mechanisms by which diet-induced alterations in microbiota influence the development of obesity. Intestinal microbiota could increase energy extraction from the diet, change the glycaemic response to food, modulate intestinal permeability and immune function, affect the release of hormones from enteroendocrine cells of the gut and directly signal to the (enteral and central) nervous system, with the hypothalamus being an important target hub in the perspective of regulation of body weight and metabolism. We discuss how this information can help to improve therapeutic strategies against obesity, targeting microbiota and its functional capabilities.

Intestinal microbiota composition associated with diet-induced obesity

Linking intestinal microbiota to obesity

The observation that the composition of the intestinal microbiota differs between obese individuals and their leaner counterparts has provided a compelling link between the intestinal microbiota and obesity development (16,26). Moreover, one of the most important breakthroughs in this field includes the discovery that adult rodents that lack microbiota (e.g. germ-free [GF] mice) are protected against DIO (27–29), although this finding could not be replicated in all animal strains and for all diets (24). Microbiota transplantations brought further insight into the role of microbiota in obesity. When microbiota of adult obese mice were inoculated into GF control mice, the obese phenotype was replicated (10,30–35), indicating that the microbiota can cause obesity in the host. These findings have stimulated investigations that seek to identify which bacteria (known as probiotics) and which food supplements that stimulate the growth of beneficial bacteria (known as prebiotics) could contribute to improve the treatment of obesity (see section "Targeting intestinal microbiota to treat obesity").

Because the microbiota is rapidly altered by diet (36–39) and the consumption of a HFD is known to cause obesity (1–3,5), it has been suggested that diet-induced alterations in microbiota could contribute to the pathogenesis of obesity. To identify potentially beneficial and detrimental bacteria for obesity development, we review the HFD-induced effects on common parameters related to obesity and on the rodent microbiota (31,32,40–60). A number of significant correlations between the human or rodent microbiota and several common parameters related to obesity have been reported (Table 1) (44,47,48,51,54,57,58,60–67,69–72). Additionally, a number of consistent associations have been reported (Table S1), including studies in which a specific bacterial taxonomic group is more abundant in situations where body weight is increased after HFD feeding in rodent models. The most important observations are summarized below.

Body weight

Body weight (BWt) is usually increased after HFD feeding, although one study found no change in BWt, possibly due to the short experimental duration in adult mice (32). Although the gram-negative, anaerobic bacterium *Akkermansia muciniphila* is related to multiple parameters of obesity (32,47,49,50,54), no correlation between this species and BWt has been reported, suggesting that *A. muciniphila* does not influence BWt (Table 1) (but note that a correlation between *A. muciniphila* and weight gain, not BWt, was found in pregnant women (73)). *Lactobacillus reuteri* and *Lactobacillus sakei* were positively correlated with body mass index in observational studies in adult humans (74), whereas other species of the genera *Bifidobacterium* and *Lactobacillus* attenuated BWt gain in intervention studies in HFD-fed mice fed specific strains of these bacterial species (60) (Table 1), indicating that they are potential candidates to protect the host from HFD-induced weight gain. Indeed, the administration of strains belonging to these genera generally decreases BWt gain after HFD feeding (see section "Targeting intestinal microbiota to treat obesity").

Table 1 Participant information. [Colour table can be viewed at wileyonlinelibrary.com]

Bacteria		BWt	A	FG	GI	I	IR	L	INFL	IP	Other	Sources
Akkermansia muciniphila (S)	Rodent		-3	-3		-2	-1	-2	-4	-1		(44,47,54,64,71)
	Human		-1									(69)
Firmicutes (P)	Human								-1			(65)
Lactobacillus (G)	Rodent	-2	-1							-1	+AgRP	(54,58,60)
	Human								-1			(65)
Clostridiales (O)	Rodent								1			(57,60)
Blautia (G)	Rodent						-1	1				(58)
Eubacterium (G)	Human						-1		-1			(65)
Flavonifractor (G)	Rodent	-1	1						1			(60)
Pseudoflavonifractor (G)	Rodent	1										(71)
Clostridiaceae (F)	Rodent					1						(58)
Clostridium (G)	Rodent	-1					-1		1	-2+1		(48,57,71)
	Human	-1		-1								(66)
Faecalibacterium prausnitzii (S)	Human	-1							-1			(65,66)
Lachnospiraceae (F)	Rodent	2	1	-1+1	1	1	2					(57,60,71)
	Human								1			(67)
Coprococcus (G)	Rodent			-1								(57)
Dorea (G)	Rodent		1		1							(60)
Marvinbryantia (G)	Rodent		1						1			(60)
Roseburia (G)	Rodent	-1	-1+1	-3	-1	1			1			(54,57,60,68)
Erysipelotrichaceae (F)	Rodent									-1		(71)
Allobaculum (G)	Rodent	-2	-1+1	-1	-1	-1	-1		-1+1			(57,60,71)
Peptococcaceae (F)	Rodent			-1								(57)
Ruminococcaceae (F)	Rodent	-1	-1	-1		-1	1		-1			(60)
Anaerotruncus (G)	Rodent	1	1	-2	1					1		(57,60,101)
	Human	-1										(66)
Anaerovorax (G)	Rodent		1						1			(60)
	Human					-1						(67)
Oscillibacter (G)	Rodent	2	1	1	1	1	1		1	1		(57,60)
Ruminococcus (G)	Rodent			-1+1								(57)
	Human			-1								(66)
Bacteroidetes (P)	Human								1			(65)
Alistipes (G)	Rodent		1		1				1			(60)
Bacteroides (G)	Rodent	-3+3	-1+4		1	-1	1				+NPY	(54,57,58,68,70,71)
	Human		-1	2	-1		-1					(65,66)
Paraprevotella (G)	Rodent								1			(60)
	Human		1									(67)
Prevotella (G)	Human			1	1							(65)
Porphyromonadaceae (F)	Rodent	-1		-1	-1							(57,68)
Barnesiella (G)	Rodent	-1+1	-1+1	-1+1	-1+1	-1+1	-1+1		-1+1			(60)
Parabacteroides (G)	Rodent	1	1									(58)
Actinobacteria (P)	Human								-1			(65)
Bifidobacterium (G)	Rodent	-3+1	-2+1		-2	-1		-1	-3			(54,60,61,71)
	Human								-6			(62,65)
Proteobacteria (P)	Rodent		1									(70)
Desulfovibrionaceae (F)	Rodent	1	1	1		1	1					(60)
Bilophila wadsworthia (S)	Rodent	1	1			1		2	1			(54,58)
Enterobacteriaceae (F)	Rodent		1									(70)

The numbers depict the amount of times the correlation with parameters of obesity was found, where positive numbers depict a positive correlation (green) and negative numbers depict a negative correlation (red). The intensity of green and red reflect the correlation strength, based upon the amount of times it was reported. Correlations were observed in caecal microbiota of DIO mice receiving prebiotics (70), caecal microbiota of DIO or control mice, supplemented with or without prebiotics (47), faecal microbiota of metformin-treated DIO mice (48), faecal microbiota of DIO rats receiving probiotics (60), faecal microbiota of DIO rats (58), caecal microbiota of DIO mice receiving prebiotics (44), faecal microbiota of elderly receiving probiotics (71), small intestinal microbiota of DIO mice receiving prebiotics and probiotics (61), faecal microbiota of pregnant obese women receiving inulin treatment (64), faecal microbiota of humans of different weight (65), faecal microbiota of healthy humans on a high-fat high-sugar diet for 4 weeks (66), caecal microbiota of DIO mice undergoing bariatric surgery (67), faecal microbiota of overweight and obese humans (63), faecal microbiota of DIO hamsters receiving prebiotic treatment (69), faecal microbiota of mice receiving different fat diets (62), faecal microbiota of DIO rats (57), caecal microbiota of DIO mice (54). The bacteria are from the phylum (P), order (O), family (F), genus (G) or species (S) level.

BWt, body weight; A, adiposity; FG, fasting serum glucose level; GI, glucose intolerance; I, fasting serum insulin level; IR, insulin resistance; L, serum leptin levels; INFL, inflammation; IP, intestinal permeability; AgRP, hypothalamic agouti-related peptide expression; NPY, hypothalamic neuropeptide Y expression.

Adiposity

The species *A. muciniphila* and *Clostridium coccoides* have been linked to decreased adiposity. In particular, *A. muciniphila* is consistently correlated to decreased adiposity in different studies (Table 1), a finding supported by intervention studies in which administration of this bacterium decreased adiposity in DIO mice, proving causality at least in experimental models (see section "Targeting intestinal microbiota to treat obesity") (47,49). Additionally, whenever the relative abundance of *C. coccoides* is decreased, adiposity is increased (41,43,50). Treatment with a prebiotic that decreases adiposity has been found to increase the relative abundance of *C. coccoides* (refer to section) (75–77). HFD-induced obesity in mice is accompanied by an increase in bacteria of the family *Lachnospiraceae* (78). In contrast, Kang and colleagues (79) showed that the anti-obesity effects of capsaicin could be partially mediated through an increased abundance of *Lachnospiraceae* in HFD-fed mice. Moreover, Menni and colleagues (80) found a lower long-term weight gain associated with this family in humans. The role of *Alistipes* spp. on adiposity is controversial because some studies suggest that it promotes obesity (Table 1, which summarizes correlation data), whereas other studies indicate that it is negatively associated with obesity (Table S1, which summarizes associative data) (48,49,81,82).

Energy intake

It was found that an increased relative abundance of Firmicutes, paired with a decreased relative abundance of Bacteroidetes, is often seen in parallel with an increased energy intake, while when energy intake is decreased, alterations in the relative abundance of Firmicutes and Bacteroidetes have not always been reported (or investigated) (31,32,44,45,47,48,50,53,58,59). This is in line with the theory proposed by Turnbaugh and colleagues, namely that there exists a link between the abundance of Firmicutes and Bacteroidetes and energy extraction (10,25,56).

Glycaemic control

Experimental rodent models have shown that high serum glucose levels after HFD feeding are often associated with a decreased relative abundance of *A. muciniphila* and *Bifidobacterium* spp. while the abundance of the genus *Oscillibacter*, which is also related to insulin resistance, is relatively increased (Table 1) (23,41,43,47,49,53,54,56,57,60,62). Additionally, *A. muciniphila* and *Oscillibacter* spp. are correlated to a decrease and increase respectively of serum glucose levels and insulin resistance (Table 1), and the administration of *A. muciniphila* (44,83), *Bifidobacterium pseudocatenulatum* CECT 7765 (43) and *Bacteroides uniformis* CECT 7771 (41) can protect from the HFD-induced deterioration of glucose and insulin homeostasis.

Leptin resistance

Excess calories taken from meals cause increased fat accumulation in adipose tissue, and this, in turn, increases the release of leptin from adipose tissue. Leptin then feeds back onto neural circuits such as in hypothalamus to reduce caloric intake. When the efficacy of leptin to act upon these circuits is decreased, leptin resistance develops. As leptin resistance increases during the development of obesity, circulating leptin becomes increasingly unable to activate leptin receptors in the hypothalamus, and therefore, food intake, BWt and serum leptin levels are increased (84). *Bifidobacterium* spp., *A. muciniphila* and *C. coccoides* are suggested to counteract leptin resistance. Both *Bifidobacterium* spp. and *A. muciniphila* are correlated to decreased serum leptin levels in DIO mice (Table 1) (54), while the administration of either *Bifidobacterium* strains or *A. muciniphila* (but also *B. uniformis* CECT 7771) ameliorated the elevated serum leptin levels in HFD-fed mice (41,43,49,55). Additionally, HFD-induced leptin resistance was improved by a single prebiotic treatment that increased the relative abundance of *Bifidobacterium* spp. as well as by a probiotic mixture containing several species of *Bifidobacterium* among others (see section "Targeting intestinal microbiota to treat obesity") (25,75,85). Similarly, when the relative abundance of *C. coccoides* is decreased, serum leptin levels are increased (41,43,50), while the supplementation of a prebiotic that increases the relative abundance of *C. coccoides* promotes leptin sensitivity (see section "Targeting intestinal microbiota to treat obesity") (75). The species *Bilophila wadsworthia* is suggested to worsen leptin resistance because increased serum leptin levels are often accompanied by an increased relative abundance of Proteobacteria and *B. wadsworthia* (31,47,58). Moreover, *B. wadsworthia* is correlated to increased serum leptin levels (Table 1).

'Obese microbiota'

In order to unravel which components of intestinal microbiota are consistently responsive to HFD feeding (and that could contribute to obesity) across studies, we sought to identify which of the bacterial taxa are relatively more (or less) abundant in rodents after HFD feeding (as summarized in Table 2). The relative abundance of these bacterial taxa could be indicators of a lean phenotype or an obese phenotype induced by HFD, although most of this evidence comes from rodent studies, and their microbiota differs to some extent from that of humans. Moreover, this type of evidence does not necessarily imply causality. The plausibility of the biological roles that some bacterial taxa could play

Table 2 Bacterial taxa of which the relative abundance was either increased or decreased after high-fat diet feeding in rodents

	References
Increased after HFD feeding	
Proteobacteria	(31,47,53,58,59)
Enterobacteriaceae	(41,43,53,58)
Desulfovibrionaceae	(41,54,58,59)
Bilophila wadsworthia	(47,54,58,62)
Clostridiales	(23,58)
Streptococcaceae	(40,45,53)
Streptococcus	(31,53)
Anaerotruncus	(23,49,53,57,62)
Coprococcus	(23,31,53,57)
Dorea	(23,49,53,60)
Flavonifractor	(31,53,57)
Lactococcus	(23,31,45,49,53,57)
Oscillibacter	(23,46,49,53,57,60,62)
Deferribacteres	(44,47,51)
Mucispirillum	(47,51,53)
Bacteroides	(41,47,49,51,53,57)
Odoribacter	(49,51,53)
Parabacteroides	(47,49,57)
Decreased after HFD feeding	
Actinobacteria	(53,59)
Bifidobacteriaceae	(40,45,53)
Bifidobacterium	(41,43,45,47,53,54,56,60)
Verrucomicrobia	(47,53)
Akkermansia muciniphila	(32,44,47,49,50,53,54,60)
Prevotellaceae	(46,53,57)
Prevotella	(31,47,51,53,54)
Barnesiella	(23,31,49,53,60)

in obesity supports, however, some of the associations reported. For example, *B. wadsworthia* is known to produce hydrogen sulphide that is cytotoxic for epithelial cells and could cause inflammation and an alteration in gut permeability (86). *Bilophila* spp. and *Oscillibacter* spp. are lipopolysaccharide-producing bacteria that theoretically could contribute to inflammation associated with obesity (87). Additionally, an 'obese microbiome' has been associated with a reduction in bacterial diversity compared with lean subjects (26,32), which could facilitate the overgrowth of potential pathogenic bacteria (also called pathobionts). Nonetheless, the mode of action of specific bacterial species associated with obesity still remains largely unknown.

Limitations

In most of the studies (excluding interventions with probiotics), it is only possible to make associations or correlations between a bacterial taxa and a biomarker of obesity. This means that no causal relationships can be made between a specific role of a given bacteria and neither the pathogenesis nor protection from obesity. Demonstrating a causal relationship would require specific interventions in individuals who have (or are at risk of developing) obesity with the specific bacteria. Second, the HFD-induced changes in microbiota are often inconsistent, likely due to differences in the experimental approaches. This can be different, for example, depending on (i) whether the microbiota was analysed in the faeces or in the intestinal contents such as the caecum; (ii) different methodologies used for sample processing such as DNA extraction or sequencing (88); (iii) the duration of the intervention with a HFD (51,54,57); (iv) the source of dietary fat (24,62,89); (v) the concentration of sucrose in the diet (23) and (vi) the initial microbiota composition and the genetic background of the animals (31,35). Additionally, a recent study found that mice from the same strain, which consumed the same diet, but reside in different facilities within Germany, had significantly different faecal microbiota (22). Because these differences likely impact on how the intestinal microbiota is modified by HFD feeding, different research groups are likely to find different microbial compositions in their animals depending on the surrounding environment. Furthermore, because all animals have been exposed to a HFD, most parameters of obesity are expected to increase, and therefore, relatively few negative controls are available (e.g. a decrease in BWt). Also, caution should be taken when analysing the correlations in Table 1 because human and animal data are combined and the correlations are often made during a specific intervention (e.g. DIO or probiotic treatment), of which the effects on microbiota are not always directly demonstrated. Bacterial taxa of which the relative abundance was either increased or decreased after HFD feeding in rodents are depicted in Table 2.

Conclusions

It seems clear that HFD feeding significantly modifies the composition of intestinal microbiota. It is suggested that *A. muciniphila*, *Bifidobacterium* spp., *B. uniformis* and *C. coccoides* may protect from obesity, based on their associations with adiposity, glycaemic control and leptin levels. Conversely, *B. wadsworthia and Oscillibacter* spp. are suggested to contribute to the pathogenesis of obesity. Moreover, bacterial taxa that become more abundant as a result of HFD feeding can be tentatively identified as contributors to an obese phenotype, predictors of the susceptibility for developing obesity and as targets for intervention to prevent or treat obesity (see section "Targeting intestinal microbiota to treat obesity"). Nevertheless, prospective studies in humans and interventions with appropriate design are still needed to establish whether or not enhancing or suppressing specific bacterial groups can prevent or treat obesity.

Mechanisms by which intestinal microbiota contribute to diet-induced obesity

There are several theories as to how alterations in the intestinal microbiota contribute to the pathogenesis of obesity.

Here, we summarize current knowledge regarding the pathways by which the intestinal microbiota is hypothesized to induce obesity, including its effects on energy extraction and absorption, intestinal permeability and the regulation and secretion of intestinal metabolites.

Energy extraction and absorption

In the aforementioned study of microbiota transplantation, mice receiving obese microbiota developed more adipose tissue than those receiving 'lean microbiota' (10). Interestingly, while food intake between groups was similar, the faecal gross energy content of recipients of obese microbiota was lower, indicating that they extracted more energy from the food they consumed (10). It is suggested that the fermentation of indigestible fibres increases energy extraction from the diet, while the microbiota also facilitates nutrient absorption. However, this is in contrast with the beneficial effects generally attributed to fibre and short-chain fatty acids (SCFAs) in weight management (see section "The regulation of the enteroendocrine system"). Therefore, it remains unknown as to why the obese microbiota has an increased capacity to harvest energy (10,28,46,55,89–94).

Intestinal permeability and inflammation

We have previously reviewed the evidence supporting an interaction between microbiota and immune system in obesity (95). The available literature suggests that there is a bloom of potentially pathogenic bacteria (such as *Escherichia coli* and *B. wadsworthia*) that results in an increased translocation of immunogenic bacterial products to the bloodstream (95). This is facilitated by increased intestinal permeability, which is associated with obesity and HFD feeding (42,96–98) and induced by dysbiosis (microbial imbalance) in the interaction between diet and intestinal inflammation (11,51,99). The accumulation of lipopolysaccharides from the surface membrane of gram-negative bacteria will activate innate and adaptive immunity, resulting in a low-grade inflammatory tone related to metabolic endotoxemia that is reflected, for example, by an increase in plasma levels of lipopolysaccharides. For more extensive information, refer to Sanz and Moya-Perez (95). Supporting this theory, GF mice receiving obese microbiota have increased intestinal permeability, intestinal inflammation and serum inflammation compared with GF mice receiving lean microbiota (31,32,100). A beneficial role for intestinal integrity is suggested for *Bifidobacterium* strains and *A. muciniphila*. The relative abundance of *A. muciniphila* is often decreased when intestinal permeability is increased (32,44,54), and *A. muciniphila* is positively correlated with decreased intestinal permeability (Table 1); also, intervention with specific *Bifidobacterium* strains decreases intestinal permeability after thermal injury (101). As intestinal permeability and systemic inflammation are related, it should come as no surprise that a decrease in the relative abundance of *A. muciniphila* is associated with increased intestinal and serum inflammation (32,44,49,54,60,68), while multiple correlations between *A. muciniphila*, *Bifidobacterium* spp. and decreased inflammation are reported (Table 1). More convincingly, the supplementation of living *A. muciniphila* or *Bifidobacterium* strains to DIO mice was shown to reduce systemic inflammation (43,47,49,53) (see section "Targeting intestinal microbiota to treat obesity"). A detrimental role is suggested for the genera *Oscillibacter* and *Flavonifractor*, because increased intestinal inflammation was observed when the relative abundance of these genera was increased. Moreover, significant correlations between *Oscillibacter*, *Flavonifractor* and increased inflammation are reported (Table 1).

Overall, obese microbiota can increase intestinal inflammation, intestinal permeability and subsequently systemic inflammation by increasing tumour necrosis factor alpha (TNFα) and interleukin 1beta (IL-1β) production by peritoneal macrophages (95). It is suggested that *A. muciniphila* and *Bifidobacterium* spp. reduce inflammation by protecting intestinal integrity (49,101), while the genera *Oscillibacter* and *Flavonifractor* increase inflammation via mechanisms that are poorly understood.

The regulation of the enteroendocrine system

Microbial fermentation of indigestible fibres produces metabolic products that include the SCFAs acetate, propionate and butyrate (85,97,102); however, this process is altered during obesity (10,33,47,50,57,60,76,77,103). SCFAs have multiple ways to protect from obesity (104) that are either mediated by activating specific receptors for nutrients that stimulate the intestinal release of the satiety-inducing hormones peptide YY (3–36) and glucagon-like peptide-1 (105–108), by decreasing systemic inflammation (93) or by signalling to the brain (see section "Interactions between microbiota and the hypothalamus"). In addition to an effect on enteroendocrine cells, SCFAs also target adipocytes, where they increase lipolysis and leptin release (102). Of SCFAs, especially butyrate exerts a trophic effect on the intestine, leading to increased villus height and crypt depth and thickened mucosal layer contributing to strengthen the intestinal barrier function, relevant to the development of metabolic disease (109). More recently, the SCFA acetate has been put forward, albeit controversially, as a trigger for the development of insulin resistance (103).

Conclusions

We identify three mechanisms via which the intestinal microbiota can influence the pathogenesis of obesity. First, the microbiota can increase energy extraction and

absorption by fermenting otherwise indigestible fibres. Second, the microbiota can influence intestinal permeability, thereby inducing or preventing metabolic endotoxemia. Finally, SCFAs interact with obesity via multiple different mechanisms, including effects on enteroendocrine secretions related to the gut barrier function (intestinal permeability), inflammation and appetite. Although three mechanisms of action are proposed, they may work simultaneously or be interrelated.

Interactions between microbiota and the hypothalamus

Linking microbiota and the role of the hypothalamus in obesity

It is known that hypothalamic inflammation, in which toll-like receptor 4 activation on microglia causes I-kappa-B-kinase beta/nuclear factor-kappa-beta signalling in neurones that are involved in energy homeostasis, can induce leptin resistance (25). Because multiple bacteria have been shown to influence leptin resistance (see section "Leptin resistance"), and the inoculation of obese microbiota alters central inflammation and hypothalamic gene expression (31), it is suggested that the microbiota may influence hypothalamic signalling. Indeed, multiple hypothalamic peptides appear to be under the influence of the microbiota, including the anorectic peptides proopiomelanocortin (POMC) (85,110), brain-derived neurotrophic factor (85,110–112) and corticotrophin-releasing factor (76,113–117) as well as the orexigenic peptides agouti-related peptide (AgRP) (85,110) and neuropeptide Y (85, 110, 112) (Table 3). Different research groups have investigated the role of the microbiota in the regulation of hypothalamic gene expression by transplantation of obese microbiota, by supplementation with probiotics and prebiotics in obese mouse models, by comparing GF and conventionally raised mice and by depleting the microbiota with antibiotics (Table 3) (76,85,110–117).

Interestingly, GF mice do not show the same hypothalamic gene profile as antibiotic-treated rodents, likely because antibiotics do not deplete all bacteria. Another explanation would be that these differences are caused by changes in the hypothalamic gene expression profile during early development, given that antibiotic-treated mice are not completely devoid of their microbiota. Although GF mice are protected from DIO (27–29), their hypothalamic gene expression profile promotes overeating (110). Indeed, GF mice usually show increased food intake (91), indicating that they are protected from obesity via mechanisms outside the hypothalamus.

The genus *Roseburia* is suggested to be related to POMC gene expression. When the relative abundance of *Roseburia* is increased in HFD-fed mice, POMC gene expression is increased (54), and when *Roseburia* abundance is decreased, it is decreased (56). Additionally, a significant correlation between *Lactobacillus* abundance and AgRP gene expression was found (Table 1) (54), likely caused by the interaction of *Lactobacillus* with vagal afferent nerves (see section "Microbiota and vagal afferent nerves").

Systemic inflammation and central inflammation

Because systemic inflammation can induce central inflammation through humoral, cellular and neural pathways (118), it is suggested that microbiota can increase central inflammation by increasing intestinal permeability and systemic inflammation. The mechanism here may include increased passage of circulating inflammatory cytokines across the blood–brain barrier (BBB) (119), stimulation of microglia (120) and/or activation of vagal afferent neurons (121,122) to induce central inflammation.

Table 3 The effects of microbiota on hypothalamic gene expression of proopiomelanonortin, brain-derived neurotrofic factor, corticotrophin-releasing factor, agouti-related peptide, neuropeptide Y, activity of the paraventricular nucleus, hypothalamic inflammation and leptin resistance in rodents

Microbiota	Author	Anorectic				Orexigenic		Inflammation	LR
		POMC	BDNF	CRF	PVN activity	AgRP	NPY		
Obese microbiota	Duca et al. 2014	–				+	+	+	
Probiotics	Ait-Belgnaoui et al. 2012			–					
	Ait-Belgnaoui et al. 2014			–					
	Yadav et al. 2013	+	+			–	–	–	
Prebiotics	So et al. 2007				–				
	Arora et al. 2012				–				
GF	Schéle et al. 2013	–	+			+	+		–
	Sudo et al. 2004			+					
	Crumeyrolle et al. 2014			+					
Antibiotics	Fröhlich et al. 2016		–				+		
	Desbonnet et al. 2015		–						
	Ait-Belgnaoui et al. 2012			–				–	

+, increased expression; –, decreased expression; POMC, proopiomelanonortin; BDNF, brain-derived neurotrofic factor; CRF, corticotrophin-releasing factor; PVN, paraventricular nucleus; AgRP, agouti-related peptide; NPY, neuropeptide Y; LR, leptin resistance; GF, germ free.

The BBB comprises a barrier of endothelial cells, separating the circulation from the functional brain (123). The intestinal barrier and BBB share a structural similarity (124) and are both influenced by the microbiota (31,32,119). As such, the BBB is more permeable in GF mice than in conventionally raised mice, an effect that could be restored by recolonization or butyrate administration (119). Apart from passing the BBB, circulating inflammatory cytokines can recruit inflammatory cells in the periphery to migrate to the brain (120,125) and activate vagal afferent neurones (126,127) to induce central inflammation.

Microbiota and microglia

Microglia of GF mice has an immature phenotype with decreased activation and inflammatory response (e.g. IL-1β, IL-6 and TNFα) (128), and therefore, it is suggested that they are under the influence of the microbiota. Interestingly, the immature phenotype of microglia as observed in GF mice could be reconstructed by the administration of antibiotics to conventionally raised mice, while the recolonization of GF mice with conventional microbiota quickly maturates microglia (128). This and other research indicates that microglial maturation and activation status is under the constant influence of the microbiota (32,116,129).

Interestingly, oral administration of a SCFA mix was shown to maturate the immature phenotype of microglia observed in GF mice via an interaction with the G-protein coupled receptor 43 (128). This indicates that SCFAs might provide a link between the microbiota and microglia. Of particular interest is the SCFA, acetate, that is able to cross the BBB to reach the brain (130–132), where it preferentially accumulates in the hypothalamus and alters POMC and AgRP gene expression (133–136). However, more recent literature opposes this view (103), and therefore, additional research is needed to confirm this.

Microbiota and vagal afferent nerves

Because the positive effects of several probiotics are abolished after vagotomy (137–140), it is suggested that the microbiota can interact with vagal afferent nerves, possibly via 5-hydroxytryptamine signalling (141). Diminished vagal nerve activity increases inflammation and obesity-like complications (reviewed by Valentin and Tracey (142)). Vagal nerve stimulation decreased food intake and BWt of rats (143), pigs (144) and humans (145). Interestingly, administration of a probiotic strain of *Lactobacillus rhamnosus* was shown to increase vagal nerve firing (146), suggesting that it may beneficially impact upon obesity. Indeed, it was observed that this *L. rhamnosus* strain protects from DIO (60,147). Because G-protein coupled receptor 41 was found to be co-localized with vagal afferent nerves (148), a contribution of SCFAs is expected. Indeed, SCFAs can stimulate 5-hydroxytryptamine secretion from enteroendocrine cells (149), while the SCFA butyrate has been shown to directly interact with vagal afferents (150). Additionally, the observed acetate-induced hyperphagia and insulin resistance were abolished in vagotomized rats and in rats treated with the parasympathetic blocker atropine (103).

Conclusion

The microbiota is capable of inducing changes in hypothalamic gene expression and altering energy homeostasis. These effects are likely mediated via microglial activation, systemic inflammation and vagal afferent nerve signalling. Although available evidence regarding the impact of the microbiota on hypothalamic gene expression is often confusing (Table 3), a general orexigenic effect is observed during HFD feeding, while an anorectic effect is observed during prebiotic and probiotic treatment. A major protective role in the interaction between the microbiota and the hypothalamus is suggested for SCFAs because they can decrease intestinal permeability, create a neuroprotective and anti-inflammatory environment in microglia and positively interact with vagal afferent nerves.

Targeting intestinal microbiota to treat obesity

Modifying microbiota

Given the evidence supporting a role for intestinal microbiota in obesity, understanding how we can beneficially modify microbiota becomes increasingly important. Usually, this is performed by the administration of live bacteria (probiotics) (151), the administration of food supplements that allow the growth of beneficial bacteria (prebiotics) (152) or the administration of drugs that modify microbiota (45,48). Moreover, the microbiota is also modified by surgery (153) and by faecal microbiota transplantation (FMT) (154).

Probiotics

Most research on probiotics focus on the species *Bifidobacterium* and *Lactobacillus* (151) because they have a long history of safe use in humans, while more recently, the species *A. muciniphila* has become of particular interest (155).

Bifidobacterium spp. are gram-positive anaerobic bacteria that are generally considered to play an anti-inflammatory role (71). It is suggested that increasing the relative abundance of *Bifidobacterium* spp. promotes intestinal integrity (101), thereby reducing bacterial translocation and metabolic endotoxemia (156,157). There are a large number of preclinical trials testing the effectiveness of different *Bifidobacterium* strains on rodent models of obesity. Some strains have shown the ability to reduce the inflammatory tone associated with HFD-induced obesity,

for example, by restoring the balance between regulatory T cells and B lymphocytes and by reducing pro-inflammatory cytokines of adaptive and innate immunity and endotoxemia (53). In addition, a few intervention studies report effects of some bifidobacterial strains on the control of body fat mass (158,159).

A. muciniphila is a gram-negative anaerobic species that specializes in the degradation of mucin into acetate, propionate and other bacterial metabolites (63,160). It is suggested that the beneficial effects of *A. muciniphila* are achieved by the provision of nutrients for growth of other bacteria (63,155,160), the production of acetate and propionate (63,160) and by decreasing intestinal permeability via the upregulation of mucin, based on rodent studies (49,161), but efficacy in humans has not been proven yet. Strains of other bacterial species such as *B. uniformis* and *Eubacterium hallii* are also being investigated for their possible application in obesity management but still at a preclinical level (162).

Lactobacillus has long since been proposed for use in the treatment of various diseases (163,164), and recently, its role in obesity has gained interest (151). A recent systematic review reports that of the 14 studies included, 9 showed decreased body weight and/or body fat, 3 did not find effect and 2 showed weight gain. It was also indicated that beneficial effects are strain dependent and cannot be generalized to the whole genus or species (165). The possible modes of action include the ability of some strains to exert anti-inflammatory effects and to modulate lipid metabolism parallel to increases in *Bifidobacterium* spp. (166). For more information on the different *Lactobacillus* species and strains and their role in BWt, it is recommended to read the informative review of Drissi and colleagues (164).

Prebiotics and other dietary components

Administration of some prebiotics, which are considered food components that "selectively stimulate the growth and/or activity(ies) of one or a limited number of microbial genus(era)/species in gut microbiota that confer(s) health benefits to the host" (152), has been shown to increase the abundance of *Bifidobacterium* spp. (152,167) and favour intestinal integrity via the production of mucin (49,59,161,168). Effectiveness of prebiotics in alleviating parameters related to obesity (e.g. body weight, glucose metabolism or appetite regulation) in humans varies, however, depending on the prebiotic and between studies (169–171). In addition, other food components, not defined as prebiotics, such as polyphenols, fish oil and whey protein, protect from obesity while often modifying the microbiota in parallel.

Inulin and oligofructose are indigestible fibres, commonly found in plants, that can be fermented by the microbiota (172). The fermentation of these indigestible fibres by the microbiota increases the concentration of acetate and propionate and protects from DIO by decreasing intestinal permeability, systemic inflammation and leptin resistance (75–77). In the microbiota, inulin supplementation was shown to increase the relative abundance of *Bifidobacterium*, *Eubacterium rectale* and *C. coccoides*, while the relative abundance of *Roseburia* was decreased (75–77,172). A recent study showed that fructans, an inulin-type prebiotic, modified human microbiota composition, changing the relative abundances of *Anaerostipes*, *Bilophila* and *Bifidobacterium* (173), although these changes have not been studied in the context of obesity.

Polyphenols found in fruits and vegetables (174) have been shown to protect from DIO, although their effects on food intake are controversial (59,175). It is suggested that polyphenols increase the secretion of mucin and remove free oxygen species, creating a beneficial environment for the bloom of the anaerobic *A. muciniphila* and ameliorating metabolic endotoxemia (59).

Fish oil, an anti-inflammatory food supplementation (176) found in fatty fish, has been reported to modify the microbiota in some studies (62,89). It is suggested that fish oil may protect from obesity partly by altering the relative abundance of *Bifidobacterium*, *Desulfovibrio* and *B. wadsworthia*, simultaneously decreasing intestinal permeability, stopping the influx of macrophages in the colon and preventing metabolic endotoxemia (62).

A HFD that has whey protein instead of casein protein protects from DIO by increasing energy expenditure (94,177), increasing the relative abundance of *Lactobacillus*, *Bifidobacterium* (168,177), *Oscillibacter* and *Mucispirillum* (177) and decreasing the relative abundance of *Turicibacter*, *Bacteroides* and *Clostridium* (177). In this regard, it is interesting to note that *Oscillibacter* has also been related to an impaired glucose homeostasis and inflammation in other studies as indicated in previous sections. An increase of this bacterium could be secondary to the effects of dietary protein and not necessarily causally involved in the protective role of casein against DIO.

Drugs

Metformin, an anti-diabetic drug that has been reported to cause weight loss in diabetic and non-diabetic obese patients (81), loses efficacy in animals when pretreated with antibiotics (49). Metformin has been shown to increase the relative abundance of *A. muciniphila* in rodents (48,49,82) and improve glucose clearance (48,49) although its impact on BWt and adiposity is different across different studies (48,49,82).

Surgery

One of the most successful treatments for obesity is bariatric surgery, especially Roux-en-Y gastric bypass (RYGB) (178). Increasing evidence suggests that RYGB alters the

composition and function of the microbiota in humans and that this may contribute to weight loss (153). RYGB was shown to alter the relative abundance of specific bacterial taxa (increasing the abundance of *A. muciniphila* [Verrucomicrobia], *Alistipes* [Bacteroidetes] and *Escherichia* [Proteobacteria]) and simultaneously to decrease food intake, BWt and adiposity and to increase acetate and propionate concentrations (179,180). Because these effects are transmissible by inoculating microbiota of mice or humans that underwent RYGB into recipient control mice (180,181), it is suggested that the microbiota is at least partially responsible for the alleviation of obesity after RYGB. In particular, a recent study demonstrated that the surgically altered microbiota reduced adiposity by reducing fat deposition and lowering utilization of carbohydrates as a fuel, in studies involving the colonization of GF mice with stools from the patients (181). The role of specific bacterial groups has not been investigated but could be expected to depend on the overall changes of the intestinal ecosystem. Future translational research is, however, needed to better underpin the possible modes of action of the microbiota in the ability of RYGB to treat obesity in humans.

Faecal microbiota transplantation

Numerous rodent studies show that the obese phenotype of DIO is transmissible via the transplantation of obese microbiota to lean microbiota-depleted recipients (10,31,32,35); however, human data are scarce. Transplantation of faecal microbiota was shown to affect BWt in humans (182), and therefore, FMT is now being considered as a treatment for obesity (154,183), proving successful in increasing insulin sensitivity in a pilot study (184).

Faecal microbiota transplantation is an interesting therapeutic strategy for experimental purposes and for cases that lack any therapeutic alternative (e.g. recurrent *Clostridium difficile* infection). However, FMT has limitations that include safety concerns as well as issues about standardization of the faecal material to be transplanted. This therapeutic strategy should be refined while progress continues regarding the identification of the specific bacteria responsible for the beneficial effects as well as the development of refined techniques for growing and reproducing them under laboratory conditions (185)

Conclusion

In conclusion, there are multiple ways to target obesity by modifying the microbiota, with most beneficial effects being related to increases in the relative abundance of *Bifidobacterium* spp. and *A. muciniphila* via administration of fibres with prebiotic-like effects. The role of other components of the gut microbiota positively associated with a lean phenotype in some observational studies in humans (e.g. *Oscillospira* spp., *Bacteroides* spp., *E. hallii*) still has to be proven by intervention studies with dietary strategies that promote their abundance and more directly by administering specific bacterial strains to humans (186). The benefits of FMT constitute a direct proof of concept that the microbiota plays a role in obesity-related alterations in humans and is a possible therapeutic target. However, more investigations on its efficacy and adverse effects in humans are required as well as progress towards the reproduction of completely controlled synthetic microbiotas.

Discussion and future perspectives

In the last 10 years, accumulating evidence has garnered about the relationship between the microbiota, the hypothalamus and obesity. Still, many questions remain about the mechanisms and implications of past observations. At first, many theories regarding the involvement of microbiota in DIO consisted of experiments in which animals had no/suppressed microbiota (GF or antibiotic-depleted) or had their microbiota boosted by a probiotic or prebiotic. Although such studies provided excellent proof of the involvement of the microbiota in multiple pathways linked to obesity development, they do not elucidate how obese microbiota influences these pathways (187). In order to unravel the mechanisms, faecal transplantation studies are more informative. Second, while it is known that microbiota of the faeces, caecum, colon, jejunum and ileum differ (51,188), little is known about the functional relevance of the microbiota per region particularly in humans due to the lack of accessibility to other than faecal samples. Third, because microbiota composition is determined by an interaction between diet and genetic predisposition (31,35), a major problem that arises in the field is that most rodent studies are carried out in genetically similar rodent strains (e.g. that all develop DIO), while human studies are carried out in obese subjects, in which the genetic background is often not investigated. Therefore, the effects of the microbiota in rodent studies may not always be translatable to the human situation. Lastly, most research on the role of specific bacteria focuses on the beneficial species as these serve therapeutic potential. Due to this, the knowledge of detrimental bacteria is limited, and the bacteria contributing to the pathogenesis of obesity are largely unknown. In this context, it is noteworthy that the specific deletion of detrimental bacteria, such as *Oscillibacter* and *B. wadsworthia*, may also have therapeutic potential.

In conclusion, it is evident that the microbiota contributes to the pathogenesis of obesity via the endocrine, immune and nervous systems. Here, we propose that the consumption of a HFD alters the microbiota to harvest more energy from the diet, increase intestinal permeability, cause inflammation and decrease the production of SCFAs. Moreover, the microbiota can increase microglial activation, alter hypothalamic energy homeostasis and increase hypothalamic

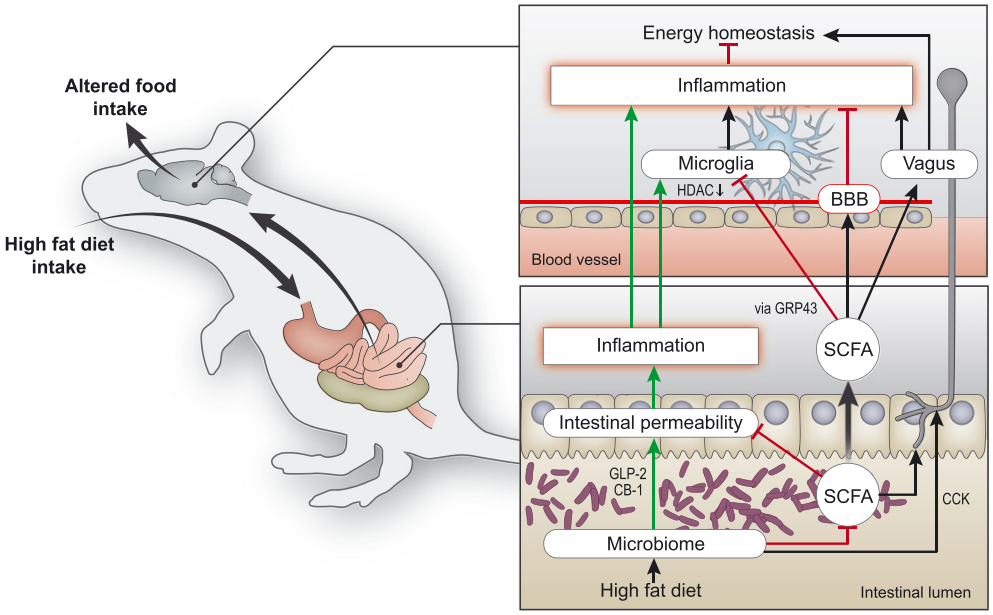

Figure 1 The proposed mechanisms of how microbiota influences energy homeostasis during high-fat diet feeding. During high-fat diet feeding, microbiota increases intestinal permeability via mechanisms involving GLP-1 and CB_1, leading to systemic inflammation. Systemic inflammation induces central inflammation via humoral, cellular (microglia) or neural (not shown) pathways, impairing energy homeostasis and increasing food intake. Short-chain fatty acid, of which the production is decreased during diet-induced obesity, promotes colonic integrity, blood–brain barrier integrity and induces a neuroprotective and anti-inflammatory state in microglia by inhibiting (HDAC, histone deacetylase) via the G-protein coupled receptor 43. Moreover, both microbiota and short-chain fatty acid interact with vagal afferent nerves, communicating with the hypothalamus about inflammation and energy homeostasis, although its influence is unclear. Red lines depict negative connections; green lines depict positive connections, and black lines depict unknown connections (CB1, cannabinoid receptor 1; CCK, cholecystokinin; GPR43, G protein-coupled receptor 43). [Colour figure can be viewed at wileyonlinelibrary.com]

inflammation via humoral, cellular and neuronal pathways (summarized in Fig. 1 and Table 1). A major protective role is proposed for SCFAs that can inhibit all the pathways contributing to the pathogenesis of obesity.

Conflict of interest statement

No conflict of interest was declared.

Acknowledgements

This work was supported by the European Union's Seventh Framework Program under grant agreements 613979 (MyNewGut to YS) and 607310 (Nudge-it, to RA and SD), by the Spanish Ministry of Economy and Competitiveness (MINECO, grant AGL2014-52101-P to YS), by the Swedish Research Council for Medicine (Vetenskapsrådet, grant number 2016-20195 to SD) and by the Dutch STW. We also acknowledge support from the European College for Neuropsychopharmacology (the Nutrition Network).

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article. https://doi.org/10.1111/obr.12661

Table S1: The high-fat diet-induced effect on faecal and caecal microbiota and parameters of obesity during different times and diets. The numbers depict the amount of times the relative abundance of a bacteria was increased (+), decreased (−), unchanged (=) or inconsistently changed (any combination of the three). The left side of the table displays the different phyla, orders and families with the genera and species that were changed during high-fat diet feeding. The top side of the table displays the different diets, duration of the studies and location of where microbiota were analysed. The bottom of the table displays the parameters of obesity and whether they were increased (arrow up), decreased (arrow down) or unchanged (arrow right). BW, body weight; A, adiposity; EI, energy intake; G, fasting serum glucose level; GI, glucose intolerance; I, fasting serum insulin level; IR, insulin resistance; L, serum leptin levels; SI, serum inflammation; II, intestinal inflammation; AI, adipose tissue inflammation; IP, intestinal permeability; POMC, hypothalamic pro-opiomelanocortin expression; AgRP, hypothalamic agouti-related peptide expression; NPY, hypothalamic neuropeptide Y expression. HFD1s = commercial, lard-based; HFD2 = home-made, lard-based; HFD3 = anhydrous milkfat-based; HFD4 = commercial, lard-based (with inulin). HFD1a = D12492 (Research Diets, New Brunswick, USA), HFD1b = D12451 (Research Diets,

New Brunswick, USA), HFD1c = TD.06414 (Envigo, New Brunswick, USA), HFD1d = AIN-76A (OpenSource Diets, New Brunswick, USA). *These animals did not consume a HFD diet, but received the microbiome from animals that developed diet-induced obesity.

References

1. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet* 2001; **357**: 505–508.
2. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr* 2004; **79**: 537–543.
3. Pereira MA, Kartashov AI, Ebbeling CB *et al*. Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. *Lancet* 2005; **365**: 36–42.
4. Apolzan J, Harris R. Differential effects of chow and purified diet on the comsumption of sucrose solution and lard and the development of obesity. *Physiol Behav* 2012; **105**: 325–331.
5. la Fleur SE, Luijendijk MCM, van der Zwaal EM, Brans MAD, Adan RAH. The snacking rat as model of human obesity: effects of a free-choice high-fat high-sugar diet on meal patterns. *Int J Obes (Lond)* 2013: 1–24.
6. Choi H-N, Kang M-J, Lee S-J, Kim J-I. Ameliorative effect of myricetin on insulin resistance in mice fed a high-fat, high-sucrose diet. *Nutr Res Pract* 2014; **8**: 544.
7. Sinasac DS, Riordan JD, Spiezio SH, Yandell BS, Croniger CM, Nadeau JH. Genetic control of obesity, glucose homeostasis, dyslipidemia and fatty liver in a mouse model of diet-induced metabolic syndrome. *Int J Obes (Lond)* 2015: 1–10.
8. De Souza CT, Araujo EP, Bordin S *et al*. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. *Endocrinology* 2005; **146**: 4192–4199.
9. Ahima R, Antwi D. Brain regulation of appetite and satiety. *Endocrinol Metab Clin North Am* 2008; **37**: 811–823.
10. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006; **444**: 1027–1031.
11. Shen J, Obin MS, Zhao L. The gut microbiota, obesity and insulin resistance. *Mol Aspects Med* 2013; **34**: 39–58.
12. Festi D, Schiumerini R, Eusebi LH, Marasco G, Taddia M, Colecchia A. Gut microbiota and metabolic syndrome. *World J Gastroenterol* 2014; **20**: 16079–16094.
13. Rosenbaum M, Knight R, Leibel RL. The gut microbiota in human energy homeostasis and obesity. *Trends Endocrinol Metab* 2015; **26**: 493–501.
14. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. [WWW document]. URL http://biorxiv.org/content/biorxiv/early/2016/01/06/036103.full.pdf
15. Qin J, Li R, Raes J *et al*. A human gut microbial gene catalog established by metagenomic sequencing. *Nature* 2010; **464**: 59–65.
16. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A* 2005; **102**: 11070–11075.
17. Hamady M, Knight R, Hamady M, Knight R. Tools, techniques, and challenges Microbial community profiling for human microbiome projects: tools, techniques, and challenges. 2009;1141–1152.
18. Tap J, Mondot S, Levenez F *et al*. Towards the human intestinal microbiota phylogenetic core. *Environ Microbiol* 2009; **11**: 2574–2584.
19. Wang J, Thingholm LB, Skiecevičienė J *et al*. Genome-wide association analysis identifies variation in vitamin D receptor and other host factors influencing the gut microbiota. *Nat Genet* 2016; **48**: 1396–1406.
20. Liu S, Weiner HL. The host shapes the gut microbiota via fecal microRNA. *Cell Host Microbe* 2016; **19**: 32–43.
21. Macke E, Tasiemski A, Massol F, Callens M, Decaestecker E. Life history and eco-evolutionary dynamics in light of the gut microbiota. *Oikos* 2017; **126**: 508–531.
22. Rausch P, Basic M, Bleich A *et al*. Analysis of factors contributing to variation in the C57BL/6J fecal microbiota across German animal facilities. *Int J Med Microbiol* 2016: 1–13.
23. Magnusson KR, Hauck L, Jeffrey BM *et al*. Relationships between diet-related changes in the gut microbiome and cognitive flexibility. *Neuroscience* 2015; **300**: 128–140.
24. Fleissner CK, Huebel N, Abd El-Bary MM, Loh G, Klaus S, Blaut M. Absence of intestinal microbiota does not protect mice from diet-induced obesity. *Br J Nutr* 2010; **104**: 919–929.
25. de Git KCG, Adan RAH. Leptin resistance in diet-induced obesity: the role of hypothalamic inflammation. *Obes Rev* 2015; **16**: 207–224.
26. Turnbaugh PJ, Hamady M, Yatsunenko T *et al*. A core gut microbiome in obese and lean twins. *Nature* 2009; **457**: 480–484.
27. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Natl Acad Sci* 2007; **104**: 979–984.
28. Rabot S, Membrez M, Bruneau A *et al*. Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. *FASEB J* 2010; **24**: 4948–4959.
29. Duca FA, Swartz TD, Sakar Y, Covasa M. Increased oral detection, but decreased intestinal signaling for fats in mice lacking gut microbiota. *PLoS One* 2012; **7**.
30. Ji Y, Sun S, Goodrich JK *et al*. Diet-induced alterations in gut microflora contribute to lethal pulmonary damage in TLR2/TLR4-deficient mice. *October* 2008; **141**: 520–529.
31. Duca FA, Sakar Y, Lepage P *et al*. Replication of obesity and associated signaling pathways through transfer of microbiota from obese-prone rats. *Diabetes* 2014; **63**: 1624–1636.
32. Bruce-Keller AJ, Michael Salbaum J, Luo M *et al*. Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity. *Biol Psychiatry* 2014; **77**: 607–615.
33. Schulz MD, Atay Ç, Heringer J *et al*. High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity. *Nature* 2015; **514**: 508–512.
34. Ellekilde M, Selfjord E, Larsen CS *et al*. Transfer of gut microbiota from lean and obese mice to antibiotic-treated mice. *Sci Rep* 2014; **4**: 5922.
35. Ridaura VK, Faith JJ, Rey FE *et al*. Cultured gut microbiota from twins discordant for obesity modulate adiposity and metabolic phenotypes in mice. *Science (80-)* 2014; **341**: 1–22.
36. De Filippo C, Cavalieri D, Di Paola M *et al*. 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**: 14691–14696.
37. Arumugam M, Raes J, Pelletier E *et al*. Enterotypes of the human gut microbiome. *Nature* 2013; **473**: 174–180.
38. Wu GD, Chen J, Hoffmann C *et al*. Linking long-term dietary patterns with gut microbial enterotypes. *Science (80-)* 2011; **334**: 105–108.

39. Ottman N, Smidt H, de Vos WM, Belzer C. The function of our microbiota: who is out there and what do they do? *Front Cell Infect Microbiol* 2012; **2**: 1–11.
40. Zhang C, Zhang M, Wang S *et al*. Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice. *ISME J* 2010; **4**: 232–241.
41. Cano PG, Santacruz A, Moya A, Sanz Y. *Bacteroides uniformis CECT 7771* ameliorates metabolic and immunological dysfunction in mice with high-fat-diet induced obesity. *PLoS One* 2012; **7**: 1–16.
42. Kim KA, Gu W, Lee IA, Joh EH, Kim DH. High fat diet-induced gut microbiota exacerbates inflammation and obesity in mice via the TLR4 signaling pathway. *PLoS One* 2012; **7**: 1–11.
43. Cano PG, Santacruz A, Trejo FM, Sanz Y. *Bifidobacterium CECT 7765* improves metabolic and immunological alterations associated with obesity in high-fat diet-fed mice. *Obesity* 2013; **21**: 2310–2321.
44. Everard A, Belzer C, Geurts L *et al*. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proc Nati Acad Sci USA* 2013; **110**: 9066–9071.
45. Murphy EF, Clarke SF, Marques TM *et al*. Antimicrobials: strategies for targeting obesity and metabolic health? *Gut Microbes* 2013; **4**: 220–226.
46. Park DY, Ahn YT, Park SH *et al*. Supplementation of *Lactobacillus curvatus KY1032* in diet-induced obese mice is associated with gut microbial changes and reduction in obesity. *PLoS One* 2013; **8**.
47. Everard A, Lazarevic V, Gaïa N *et al*. Microbiome of prebiotic-treated mice reveals novel targets involved in host response during obesity. *ISME J* 2014; **8**: 2116–2130.
48. Lee H. Effect of metformin on metabolic improvement and gut microbiota. *Appl Environ Microbiol* 2014; **80**: 5935–5943.
49. Shin N-R, Lee J-C, Lee H-Y *et al*. An increase in the *Akkermansia* spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut* 2014; **63**: 727–735.
50. Alard J, Lehrter V, Rhimi M *et al*. Beneficial metabolic effects of selected probiotics on diet-induced obesity and insulin resistance in mice are associated with improvement of dysbiotic gut microbiota. *Environ Microbiol* 2016; **18**: 1484–1497.
51. Hamilton MK, Boudry G, Lemay DG, Raybould HE. Changes in intestinal barrier function and gut microbiota in high-fat diet-fed rats are dynamic and region dependent. *Am J Physiol Gastrointest Liver Physiol* 2015; **308**: G840–G851.
52. Hwang I, Park YJ, Kim YR *et al*. Alteration of gut microbiota by vancomycin and bacitracin improves insulin resistance via glucagon-like peptide 1 in diet-induced obesity. *FASEB J* 2015; **29**: 2397–2411.
53. Moya-Pérez A, Neef A, Sanz Y. *Bifidobacterium pseudocatenulatum CECT 7765* reduces obesity-associated inflammation by restoring the lymphocyte-macrophage balance and gut microbiota structure in high-fat diet-fed mice. *PLoS One* 2015; **10**: 1–28.
54. Schneeberger M, Everard A, Gómez-Valadés AG *et al*. *Akkermansia muciniphila* inversely correlates with the onset of inflammation, altered adipose tissue metabolism and metabolic disorders during obesity in mice. *Sci Rep* 2015; **5**: 16643.
55. Wu CC, Weng WL, Lai WL *et al*. Effect of *lactobacillus plantarum strain K21* on high-fat diet-fed obese mice. *Evidence-based Complement Altern Med* 2015; **2015**: 1–9.
56. Khare P, Jagtap S, Jain Y *et al*. Cinnamaldehyde supplementation prevents fasting-induced hyperphagia, lipid accumulation, and inflammation in high-fat diet-fed mice. *Biofactors* 2016 In press.
57. Lin H, An Y, Hao F, Wang Y, Tang H. Correlations of fecal metabonomic and microbiomic changes induced by high-fat diet in the pre-obesity state. *Sci Rep* 2016; **6**: 21618.
58. Lecomte V, Kaakoush NO, Maloney CA *et al*. Changes in gut microbiota in rats fed a high fat diet correlate with obesity-associated metabolic parameters. *PLoS One* 2015; **10**: 1–22.
59. Roopchand DE, Carmody RN, Kuhn P *et al*. Dietary polyphenols promote growth of the gut bacterium *Akkermansia muciniphila* and attenuate high-fat diet-induced metabolic syndrome. *Diabetes* 2015; **64**: 2847–2858.
60. Wang J, Tang H, Zhang C *et al*. Modulation of gut microbiota during probiotic-mediated attenuation of metabolic syndrome in high fat diet-fed mice. *ISME J* 2015; **9**: 1–15.
61. Axling U, Olsson C, Xu J *et al*. Green tea powder and *Lactobacillus plantarum* affect gut microbiota, lipid metabolism and inflammation in high-fat fed C57BL/6J mice. *Nutr Metab (Lond)* 2012; **9**: 105.
62. Lam YY, Ha CWY, Hoffmann JMA *et al*. Effects of dietary fat profile on gut permeability and microbiota and their relationships with metabolic changes in mice. *Obesity* 2015; **23**: 1429–1439.
63. Dao MC, Everard A, Aron-Wisnewsky J *et al*. *Akkermansia muciniphila* and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut* 2015: 1–11.
64. Dewulf EM, Cani PD, Claus SP *et al*. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. *Gut* 2012; **62**: 1112–1121.
65. Zupancic ML, Cantarel BL, Liu Z *et al*. Analysis of the gut microbiota in the old order amish and its relation to the metabolic syndrome. *PLoS One* 2012; **7**: 1–10.
66. Kelder T, Stroeve JHM, Bijlsma S, Radonjic M, Roeselers G. Correlation network analysis reveals relationships between diet-induced changes in human gut microbiota and metabolic health. *Nutr Diabetes* 2014; **4**: e122.
67. Ryan KK, Tremaroli V, Clemmensen C *et al*. FXR is a molecular target for the effects of vertical sleeve gastrectomy. *Nature* 2014; **509**: 183–188.
68. Lam YY, Ha CW, Campbell CR *et al*. Increased gut permeability and microbiota change associate with mesentereic fat inflammation and metabolic dysfunction in diet-induced obese mice. *PloS* 2012; **7**: 1–10.
69. Kim H, Kim DH, Seo KH *et al*. Modulation of the intestinal microbiota is associated with lower plasma cholesterol and weight gain in hamsters fed chardonnay grape seed flour. *J Agric Food Chem* 2015; **63**: 1460–1467.
70. Cani PD, Neyrinck AM, Fava F *et al*. Selective increases of *bifidobacteria* in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia* 2007; **50**: 2374–2383.
71. Ouwehand AC, Bergsma N, Parhiala R *et al*. *Bifidobacterium* microbiota and parameters of immune function in elderly subjects. *FEMS Immunol Med Microbiol* 2008; **53**: 18–25.
72. Larsen N, Vogensen FK, Van Den Berg FWJ *et al*. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* 2010; **5**: 1–10.
73. Santacruz A, Collado MC, García-Valdés L, et al. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *Br J Nutr* 2010; **104**: 83–92.
74. Million M, Thuny F, Angelakis E *et al*. *Lactobacillus reuteri* and *Escherichia coli* in the human gut microbiota may predict weight gain associated with vancomycin treatment. *Nutr Diabetes* 2013; **3**: e87.

75. Everard A, Lazarevic V, Derrien M *et al*. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes* 2011; **60**: 2775–2786.
76. Arora T, Loo RL, Anastasovska J *et al*. Differential effects of two fermentable carbohydrates on central appetite regulation and body composition. *PLoS One* 2012; **7**: 1–10.
77. Anastasovska J, Arora T, Sanchez Canon GJ *et al*. Fermentable carbohydrate alters hypothalamic neuronal activity and protects against the obesogenic environment. *Obesity* 2012; **20**: 1016–1023.
78. Zeng H, Ishaq SL, Zhao FQ, Wright ADG. Colonic inflammation accompanies an increase of β-catenin signaling and Lachnospiraceae/Streptococcaceae bacteria in the hind gut of high-fat diet-fed mice. *J Nutr Biochem* 2016; **35**: 30–36.
79. Kang C, Wang B, Kaliannan K *et al*. Gut microbiota mediates the protective effects of dietary capsaicin against chronic low-grade inflammation and associated obesity induced by high-fat diet. *Am Soc Microbiol* 2017; **8**: 1–14.
80. Menni C, Jackson MA, Pallister T, Steves CJ, Spector TD, Valdes AM. Gut microbiome diversity and high-fibre intake are related to lower long-term weight gain. *Int J Obes (Lond)* 2017; **41**: 1099–1105.
81. Golay A. Metformin and body weight. *Int J Obes (Lond)* 2008; **32**: 61–72.
82. Zhang X, Zhao Y, Xu J *et al*. Modulation of gut microbiota by berberine and metformin during the treatment of high-fat diet-induced obesity in rats. *Sci Rep* 2015; **5**: 14405.
83. Plovier H, Everard A, Druart C *et al*. A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nat Publ Gr* 2016; **23**: 107–113.
84. Morris D, Rui L. Recent advances in understanding leptin signaling and leptin resistance. *Am J Physiol Endocrinol Metab* 2009; **297**: 1247–1259.
85. Yadav H, Lee JH, Lloyd J, Walter P, Rane SG. Beneficial metabolic effects of a probiotic via butyrate-induced GLP-1 hormone secretion. *J Biol Chem* 2013; **288**: 25088–25097.
86. Devkota S, Wang Y, Musch M, Leone V, Fehlner-peach H. Dietary fat-induced taurocholic acid production promotes pathobiont and colitis in IL-10−/− mice. *Nature* 2012; **487**: 104–108.
87. Song JJ, Tian WJ, Kwok L-Y *et al*. Effects of microencapsulated *Lactobacillus plantarum LIP-1* on the gut microbiota of hyperlipidaemic rats. *Br J Nutr* 2017; **118**: 481–492.
88. Tourlousse DM, Yoshiike S, Ohashi A, Matsukura S, Noda N, Sekiguchi Y. Synthetic spike-in standards for high-throughput 16S rRNA gene amplicon sequencing. *Nucleic Acids Res* 2017; **45**: e23.
89. Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Bäckhed F. Crosstalk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. *Cell Metab* 2015; **22**: 658–668.
90. Miller TL, Wolin MJ. Pathways of acetate, propionate, and butyrate formation by the human fecal microbial flora. *Appl Environ Microbiol* 1996; **62**: 1589–1592.
91. Bäckhed F, Ding H, Wang T *et al*. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A* 2004; **101**: 15718–15723.
92. Semova I, Carten JD, Stombaugh J *et al*. Microbiota regulate intestinal absorption and metabolism of fatty acids in the zebrafish. *Cell Host Microbe* 2013; **12**: 277–288.
93. Vinolo M A. R, Rodrigues HG, Festuccia WT, *et al*. Tributyrin attenuates obesity-associated inflammation and insulin resistance in high-fat-fed mice. *AJP Endocrinol Metab* 2012;**303**:E272–E282.
94. Tranberg B, Hellgren LI, Lykkesfeldt J *et al*. Whey protein reduces early life weight gain in mice fed a high-fat diet. *PLoS One* 2013; **8**: 1–7.
95. Sanz Y, Moya-Pérez A. Microbiota, inflammation and obesity. *Adv Exp Med Biol* 2014; **817**: 291–317.
96. Muccioli GG, Naslain D, Bäckhed F *et al*. The endocannabinoid system links gut microbiota to adipogenesis. *Mol Syst Biol* 2010; **6**: 392.
97. Lim S, Jeong J, Woo KH, Han MJ, Kim H. *Lactobacillus sakei OK67* ameliorates high-fat diet-induced blood glucose intolerance and obesity in mice by inhibiting gut microbiota LPS production and inducing colon tight junction protein expression. *Nutr Res* 2015; **36**: 337–348.
98. de La Serre CB, Ellis CL, Lee J *et al*. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. *Am J Physiol Gastrointest Liver Physiol* 2010; **299**: G440–G448.
99. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG. Breaking down the barriers : the gut microbiome, intestinal permeability and stress-related psychiatric. 2015; **9**: 1–20.
100. Ding S, Chi MM, Scull BP *et al*. High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. *PLoS One* 2010; **5**.
101. Wang Z, Xiao G, Yao Y, Guo S, Lu K, Sheng Z. The role of *bifidobacteria* in gut barrier function after thermal injury in rats. *J Trauma* 2006; **61**: 650–657.
102. Kumari M, Kozyrskyj AL. Gut microbial metabolism defines host metabolism: an emerging perspective in obesity and allergic inflammation. *Obes Rev* 2017; **18**: 18–31.
103. Perry RJ, Peng L, Barry NA *et al*. Acetate mediates a microbiome-brain-β cell axis promoting metabolic syndrome. *Nature* 2016; **534**: 213–217.
104. Chakraborti CK. New-found link between microbiota and obesity. *World J Gastrointest Pathophysiol* 2015; **6**: 110–119.
105. Samuel BS, Shaito A, Motoike T *et al*. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci* 2008; **105**: 16767–16772.
106. Chambers ES, Viardot A, Psichas A *et al*. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. *Gut* 2015; **64**: 1744–1754.
107. Psichas A, Sleeth ML, Murphy KG *et al*. The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. *Int J Obes (Lond)* 2015; **39**: 424–429.
108. Mishra AK, Dubey V, Ghosh AR. Obesity: an overview of possible role(s) of gut hormones, lipid sensing and gut microbiota. *Metabolism* 2016; **65**: 48–65.
109. Brahe LK, Astrup A, Larsen LH. Is butyrate the link between diet, intestinal microbiota and obesity-related metabolic diseases? *Obes Rev* 2013; **14**: 950–959.
110. Schéle E, Grahnemo L, Anesten F, Hallén A, Bäkhed F, Jansson JO. The gut microbiota reduces leptin sensitivity and the expression of the obesity-suppressing neuropeptides proglucagon (Gcg) and brain-derived neurotrophic factor (Bdnf) in the central nervous system. *Endocrinology* 2013; **154**: 3643–3651.
111. Desbonnet L, Clarke G, Traplin A *et al*. Gut microbiota depletion from early adolescence in mice: implications for brain and behaviour. *Brain Behav Immun* 2015; **48**: 165–173.
112. Fröhlich EE, Farzi A, Mayerhofer R *et al*. Cognitive impairment by antibiotic-induced gut dysbiosis: analysis of gut microbiota-brain communication. *Brain Behav Immun* 2016; **56**: 140–155.

113. Sudo N, Chida Y, Aiba Y *et al*. Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. *J Physiol* 2004; **5581**: 263–275.
114. So PW, Yu WS, Kuo YT *et al*. Impact of resistant starch on body fat patterning and central appetite regulation. *PLoS One* 2007; **2**: 1–8.
115. Ait-Belgnaoui A, Durand H, Cartier C *et al*. Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology* 2012; **37**: 1885–1895.
116. Ait-Belgnaoui A, Colom A, Braniste V *et al*. Probiotic gut effect prevents the chronic psychological stress-induced brain activity abnormality in mice. *Neurogastroenterol Motil* 2014; **26**: 510–520.
117. Crumeyrolle-Arias M, Jaglin M, Bruneau A *et al*. Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats. *Psychoneuroendocrinology* 2014; **42**: 207–217.
118. Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol Ther* 2011; **130**: 226–238.
119. Braniste V, Al-Asmakh M, Kowal C *et al*. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med* 2014; **6**: 263ra158–263ra158.
120. D'Mello C, Le T, Swain MG. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factor signaling during peripheral organ inflammation. *J Neurosci* 2009; **29**: 2089–2102.
121. de La Serre CB, de Lartigue G, Raybould HE. Chronic exposure to low dose bacterial lipopolysaccharide inhibits leptin signaling in vagal afferent neurons. *Physiol Behav* 2015; **139**: 188–194.
122. Waise TMZ, Toshinai K, Naznin F *et al*. One-day high-fat diet induces inflammation in the nodose ganglion and hypothalamus of mice. *Biochem Biophys Res Commun* 2015; **464**: 1157–1162.
123. Bauer HC, Krizbai IA, Bauer H, Traweger A. "You shall not pass"—tight junctions of the blood brain barrier. *Front Neurosci* 2014; **8**: 1–21.
124. Doran KS, Banerjee A, Disson O, Lecuit M. Concepts and mechanisms: crossing host barriers. *Cold Spring Harb Perspect Med* 2013; **3**: 1–19.
125. Kerfoot SM, D'Mello C, Nguyen H *et al*. TNF-a-secreting monocytes are recruited into the brain of cholestatic mice. *Hepatology* 2006; **43**: 154–162.
126. Holzer P, Danzer M, Schicho R, Samberger C, Painsipp E, Lippe IT. Vagal afferent input from the acid-challenged rat stomach to the brainstem: Enhancement by interleukin-1β. *Neuroscience* 2004; **129**: 439–445.
127. Luheshi GN, Bluthé RM, Rushforth D *et al*. Vagotomy attenuates the behavioural but not the pyrogenic effects of interleukin-1 in rats. *Auton Neurosci Basic Clin* 2000; **85**: 127–132.
128. Erny D, Hrabě de Angelis AL, Jaitin D *et al*. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci* 2015; **18**: 965–977.
129. D'Mello C, Ronaghan N, Zaheer R *et al*. Probiotics improve inflammation-associated sickness behavior by altering communication between the peripheral immune system and the brain. *J Neurosci* 2015; **35**: 10821–10830.
130. Mathew R, Arun P, Madhavarao CN, Moffett JR, Namboodiri MA. Progress toward acetate supplementation therapy for Canavan disease: glyceryl triacetate administration increases acetate, but not N-acetylaspartate, levels in brain. *J Pharmacol Exp Ther* 2005; **315**: 297–303.
131. Song WS, Nielson BR, Banks KP, Bradley YC. Normal organ standard uptake values in carbon-11 acetate PET imaging. *Nucl Med Commun* 2009; **30**: 462–465.
132. Deelchand DK, Shestov AA, Koski DM, Uğurbil K, Henry PG. Acetate transport and utilization in the rat brain. *J Neurochem* 2009; **109**: 46–54.
133. Frost G, Sleeth ML, Sahuri-Arisoylu M *et al*. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. *Nat Commun* 2014; **5**: 3611.
134. Reisenauer CJ, Bhatt DP, Mitteness DJ, Slanczka ER, Gienger HM, Watt JART. Acetate supplementation attenuates lipopolysaccharide-induced neuroinflammation. *J Neurochem* 2011; **117**: 264–274.
135. Soliman ML, Smith MD, Houdek HM, Rosenberger TA. Acetate supplementation modulates brain histone acetylation and decreases interleukin-1β expression in a rat model of neuroinflammation. *J Neuroinflammation* 2012; **9**: 51.
136. Brissette C, Houdek HM, Floden AM, Rosenberger TA. Acetate supplementation reduces microglia activation and brain interleukin-1β levels in a rat model of Lyme neuroborreliosis. *J Neuroinflammation* 2012; **9**: 249.
137. Bercik P, Park AJ, Sinclair D *et al*. The anxiolytic effect of *Bifidobacterium longum NCC3001* involves vagal pathways for gut-brain communication. *Neurogastroenterol Motil* 2011; **23**: 1132–1139.
138. Tanida M, Nagai K. Electrophysiological analysis of the mechanism of autonomic action by *lactobacilli*. *Biosci microflora* 2011; **30**: 99–109.
139. Bravo JA, Forsythe P, Chew MV *et al*. 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**: 16050–16055.
140. Malick M, Gilbert K, Daniel J *et al*. Vagotomy prevents the effect of probiotics on caspase activity in a model of postmyocardial infarction depression. *Neurogastroenterol Motil* 2015; **27**: 663–671.
141. Horii Y, Nakakita Y, Fujisaki Y *et al*. Effects of intraduodenal injection of *Lactobacillus brevis SBC8803* on autonomic neurotransmission and appetite in rodents. *Neurosci Lett* 2013; **539**: 32–37.
142. Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex: linking immunity and metabolism. *Nat Rev Endocrinol* 2012; **8**: 743–754.
143. Bugajski A, Gil K, Ziomber A, Zurowski D, Zaraska W, Thor P. Effect of long-term vagal stimulation on food intake and body weight during diet induced obesity in rats. *J Physiol Pharmacol* 2007; **56**: 5–12.
144. Val-Laillet D, Biraben A, Randuineau G, Malbert CH. Chronic vagus nerve stimulation decreased weight gain, food consumption and sweet craving in adult obese minipigs. *Appetite* 2010; **55**: 245–252.
145. Pardo J, Sheikh S, Kuskowski M *et al*. Weight loss during chronic, cervical vagus nerve stimulation in despressed patients with obesity. *October*. 2007; **31**: 1756–1759.
146. Perez-Burgos A, Wang B, Mao Y-K *et al*. Psychoactive bacteria *Lactobacillus rhamnosus (JB-1)* elicits rapid frequency facilitation in vagal afferents. *Am J Physiol Gastrointest Liver Physiol* 2013; **304**: G211–G220.
147. Park K-Y, Kim B, Hyun C-K. *Lactobacillus rhamnosus GG* improves glucose tolerance through alleviating ER stress and suppressing macrophage activation in db/db mice. *J Clin Biochem Nutr* 2015; **56**: 240–246.
148. De Vadder F, Kovatcheva-Datchary P, Goncalves D *et al*. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell* 2014; **156**: 84–96.

149. Fukumoto S, Tatewaki M, Yamada T *et al*. Short-chain fatty acids stimulate colonic transit via intraluminal 5-HT release in rats. *Am J Physiol Regul Integr Comp Physiol* 2003; **284**: R1269–R1276.
150. Lal S, Kirkup AJ, Brunsden AM, Thompson DG, Grundy D. Vagal afferent responses to fatty acids of different chain length in the rat. *Am J Physiol Gastrointest Liver Physiol* 2001; **281**: G907–G915.
151. Nova E, Perez de Heredia F, Gomez-Martinez S, Marcos A. The role of probiotics on the microbiota: effect on obesity. *Nutr Clin Pract* 2016; **31**: 387–400.
152. Roberfroid M, Gibson GR, Hoyles L *et al*. Prebiotic effects: metabolic and health benefits. *Br J Nutr* 2010; **104**: S1–63.
153. Kong L-C, Tap J, Aron-Wisnewsky J *et al*. Gut microbiota after gastric bypass in human obesity: increased richness and associations of bacterial genera with adipose tissue genes. *Am Soc Nutr* 2013; **98**: 16–24.
154. Gupta S, Allen-Vercoe E, Petrof EO. Fecal microbiota transplantation: in perspective. *Therap Adv Gastroenterol* 2015; **9**: 229–239.
155. Derrien M, Belzer C, de Vos W. *Akkermansia muciniphila* and its role in regulating host functions. *Microb Pathog* 2016; **106**: 171–181.
156. Cani PD, Possemiers S, Van de Wiele T *et al*. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 2009; **58**: 1091–1103.
157. Blaut M, Bischoff SC. Probiotics and obesity. *Ann Nutr Metab* 2010; **57**: 20–23.
158. Stenman LK, Lehtinen MJ, Meland N *et al*. Probiotic with or without fiber controls body fat mass, associated with serum zonulin, in overweight and obese adults—randomized controlled trial. *EBioMedicine* 2016; **13**: 190–200.
159. Bernini LJ, Simão ANC, Alfieri DF *et al*. Beneficial effects of *Bifidobacterium lactis* on lipid profile and cytokines in patients with metabolic syndrome: a randomized trial. Effects of probiotics on metabolic syndrome. *Nutrition* 2016; **32**: 716–719.
160. Derrien M, Vaughan EE, Plugge CM, de Vos WM. *Akkermansia muniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. *Int J Syst Evol Microbiol* 2004; **54**: 1469–1476.
161. Van der Sluis M, De Koning BAE, De Bruijn ACJM *et al*. Muc2-deficient mice spontaneously develop colitis, indicating that MUC2 is critical for colonic protection. *Gastroenterology* 2006; **131**: 117–129.
162. Romaní-Pérez M, Agusti A, Sanz Y. Innovation in microbiome-based strategies for promoting metabolic health. *Curr Opin Clin Nutr Metab Care* 2017; **20**: 1.
163. Di Cerbo A, Palmieri B, Aponte M, Morales-Medina JC, Iannitti T. Mechanisms and therapeutic effectiveness of *lactobacilli*. *J Clin Pathol* 2015: 1–17.
164. Drissi F, Raoult D, Merhej V. Metabolic role of *lactobacilli* in weight modification in humans and animals. *Microb Pathog* 2016; **106**: 182–194.
165. Crovesy L, Ostrowski M, Ferreira DMTP, Rosado EL, Soares-Mota M. Effect of *Lactobacillus* on body weight and body fat in overweight subjects: a systematic review of randomized controlled clinical trials. *Int J Obes (Lond)* 2017: 1–8.
166. Nagata S, Chiba Y, Wang C, Yamashiro Y. The effects of the *Lactobacillus casei* strain on obesity in children: a pilot study. *Benef Microbes* 2017; **8**: 535–543.
167. Delzenne NM, Neyrinck AM, Bäckhed F, Cani PD. Targeting gut microbiota in obesity: effects of prebiotics and probiotics. *Nat Rev Endocrinol* 2011; **7**: 639–646.
168. Sprong RC, Schonewille AJ, van der Meer R. Dietary cheese whey protein protects rats against mild dextran sulfate sodium-induced colitis: role of mucin and microbiota. *J Dairy Sci* 2010; **93**: 1364–1371.
169. Canfora EE, van der Beek CM, Hermes GDA *et al*. Supplementation of diet with galacto-oligosaccharides increases *Bifidobacteria*, but not insulin sensitivity, in obese prediabetic individuals. *Gastroenterology* 2017; **153**: 87–97.e3.
170. Nicolucci AC, Hume MP, Martínez I, Mayengbam S, Walter J, Reimer RA. Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity. *Gastroenterology* 2017; **153**: 711–722.
171. Hume MP, Nicolucci AC, Reimer RA. Prebiotic supplementation improves appetite control in children with overweight and obesity: a randomized controlled trial. *Am J Clin Nutr* 2017; **105**: 790–799.
172. Niness KR. Nutritional and health benefits of inulin and oligofructose. *J Nutr* 1999; **129**: 1402S–1406S.
173. Vandeputte D, Falony G, Vieira-Silva S *et al*. Prebiotic inulin-type fructans induce specific changes in the human gut microbiota. *Gut* 2017 gutjnl-2016-313271.
174. Crozier A, Jaganath I, Clifford M. Dietary phenolics: chemistry, bioavailability and effects on health. *Nat Prod Rep* 2009; **26**: 1001–1043.
175. Anhê FF, Roy D, Pilon G *et al*. A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased *Akkermansia* spp. population in the gut microbiota of mice. *Gut* 2015; **64**: 872–883.
176. Maroon JC, Bost JW. Omega-3 fatty acids (fish oil) as an anti-inflammatory: an alternative to nonsteroidal anti-inflammatory drugs for discogenic pain. *Surg Neurol* 2006; **65**: 326–331.
177. McAllan L, Skuse P, Cotter PD *et al*. Protein quality and the protein to carbohydrate ratio within a high fat diet influences energy balance and the gut microbiota In C57BL/6J mice. *PLoS One* 2014; **9**: e88904.
178. Lutz TA, Bueter M. The physiology underlying Roux-en-Y gastric bypass: a status report. *Am J Physiol Regul Integr Comp Physiol* 2014; **307**: R1275–R1291.
179. Li JV, Ashrafian H, Bueter M, Kinross J, Sands C. Metabolic surgery profoundly influences gut microbial-host metabolic crosstalk. 2013; **60**: 1214–1223.
180. Liou AP, Paziuk M, Luevano J-M Jr, Machineni S, Turnbaugh PJ, Kaplan LM. Conserved shifts in the gut microbioa due to gastric bypass reduce host weight and adiposity. 2013; **5**: 1–23.
181. Tremaroli V, Karlsson F, Werling M *et al*. Roux-en-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. *Cell Metab* 2015; **22**: 228–238.
182. Alang N, Kelly C. Weight gain after fecal microbiota transplantation. *Ofid* 2015; **2**: 1–2.
183. Jayasinghe TN, Chiavaroli V, Holland DJ, Cutfield WS, O'Sullivan JM. The new era of treatment for obesity and metabolic disorders: evidence and expectations for gut microbiome transplantation. *Front Cell Infect Microbiol* 2016; **6**: 1–11.
184. Vrieze A, Van Nood E, Holleman F *et al*. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 2012; **143**: 913–916.e7.
185. Neef A, Sanz Y. Future for probiotic science in functional food and dietary supplement development. *Curr Opin Clin Nutr Metab Care* 2013; **16**: 679–687.

186. Konikoff T, Gophna U. *Oscillospira*: a central, enigmatic component of the human gut microbiota. *Trends Microbiol* 2016; **24**: 523–524.
187. Luczynski P, McVey Neufeld K-A, Seira Oriach C, Clarke G, Dinan TG, Cryan JF. Growing up in a bubble: using germ-free animals to assess the influence of the gut microbiota on brain and behaviour. *Int J Neuropsychopharmacol* 2016: 1–31.
188. Pang W, Vogensen FK, Nielsen DS, Hansen AK. Faecal and caecal microbiota profiles of mice do not cluster in the same way. *Lab Anim* 2012; **46**: 231–236.