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Etiology and Pathophysiology

Gut microbial adaptation to dietary consumption of fructose, artificial sweeteners and sugar alcohols: implications for host–microbe interactions contributing to obesity

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Summary

The Western diet, comprised of highly refined carbohydrates and fat but reduced complex plant polysaccharides, has been attributed to the prevalence of obesity. A concomitant rise in the consumption of fructose and sugar substitutes such as sugar alcohols, artificial sweeteners, even rare sugars, has mirrored this trend, as both probable contributor and solution to the epidemic. Acknowledgement of the gut microbiota as a factor involved in obesity has sparked much controversy as to the cause and consequence of this relationship. Dietary intakes are a known modulator of gut microbial phylogeny and metabolic activity, frequently exploited to stimulate beneficial bacteria, promoting health benefits. Comparably little research exists on the impact of 'unconscious' dietary modulation on the resident commensal community mediated by increased fructose and sugar substitute consumption. This review highlights mechanisms of potential host and gut microbial fructose and sugar substitute metabolism. Evidence is presented suggesting these sugar compounds, particularly fructose, condition the microbiota, resulting in acquisition of a westernized microbiome with altered metabolic capacity. Disturbances in host–microbe interactions resulting from fructose consumption are also explored.

Keywords: Fructose, gut microbiota, malabsorption, obesity.

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Introduction

Increased prevalence of the Western diet, characterized by high fat and refined carbohydrate and sugar content, has paralleled the global incidence of obesity (1,2). A potential main contributor to the westernization of our diets and subsequent rise in obesity is the substitution of sucrose by cheaper corn-derived, fructose-saturated sweeteners (3). Conversely, replacement of sucrose by calorie-reduced (e.g. sugar alcohols) or calorie-deficient artificial and natural (e.g. Stevioside) sugar substitutes has gained popularity as a weight management strategy (4–6). Changes in sugar source and load directly impact regulation and homeostatic maintenance of host energy balance mediated by gut- and adipocyte-secreted hormones as well as the innate immune system (7–9). The human gastrointestinal (GI) tract is a complex organ comprised of both human and microbial genetic power, encoding a multitude of processes related to digestion, absorption and metabolism of dietary compounds (10,11). A potential link between the commensal flora and obesity was suggested in the early 1980s after observed changes to gut microbiota composition following weight loss induced by bypass surgery (12). The concept gained in popularity following the landmark study of Ley

et al. in 2005 where obesity was ascribed to harbouring a higher Firmicutes : Bacteroidetes ratio (13). A collective effort attempting to identify the 'obese' microbiome ensued shortly thereafter, resulting in numerous publications both supporting and refuting the relevance of the *Firmicutes* : *Bacteroidetes* ratio (14–16). Despite the body of research aimed at unravelling the relationship between obesity and the gut microbiota, it remains largely a cause or consequence question.

The aim of this review is to discuss the potential impact increased fructose and reduced calorie and calorie-free sugar substitutes are imparting on the gut microbiota and possible consequences of additional host energy gain arising from microbial metabolism of these compounds. Particular emphasis will be made on the contribution of fructose conditioning of the gut microbiota in redefining microbial community structures and metabolic activity, promoting perturbed host–microbe interactions related to obesity.

The commensal microbiota: a diverse organ with many metabolic capacities

The colon is the most densely inhabited microbial environment with roughly 10^{11} microbes g^{-1} gut content (17). Culture-independent molecular analysis of 16S rRNA, aided by development of Sanger and 454 pyrosequencing technology, has identified >1,000 microbial species belonging to >50 microbial phyla (18,19). Despite this rich diversity, the Bacteroidetes, Actinobacteria, Firmicutes and Proteobacteria phyla predominate (18,19). Gut microbial phylogeny has recently been proposed a novel classification scheme based upon the level of variation in one of three genera: *Bacteroides* (enterotype 1), *Prevotella* (enterotype 2) or *Ruminococcus* (enterotype 3) (20). Enterotypes are defined by the metabolic capacities encoded by the collective set of microbes within, which form specialized ecological niches of tightly regulated cross-feeding hierarchies (20). Enterotype 1 species related to *Bacteroides* possess a broad saccharolytic arsenal consisting of galactosidases, hexosaminidases and proteases combined with complete glycolysis and pentose phosphate pathways (20,21). Enterotype 2 is additionally enriched in *Desulfovibrio*, a genera of sulphate-reducing bacteria. The co-occurrence of *Prevotella* and *Desulfovibrio* suggests evolution of a mucin-degrading niche whereby the sulphate liberated during *Prevotella*-mediated mucin degradation is removed by *Desulfovibrio*, a process necessary to prevent sulphate inhibition of mucin degradation (20). Enterotype 3 members of *Lachnospiraceae* family are butyrate-producing bacteria and are characterized by a combination of mucin-degrading and sugar uptake machinery, accounting for their ability to ferment a wide range of substrate (20). This combined genetically encoded metabolic diversity is essential for metabolizing the otherwise indigestible dietary carbohydrate and starch (22). Microbial fermentation of hydrolyzed carbohydrates and simple sugars results in production of short-chain fatty acid (SCFA) butyrate, acetate and propionate, providing an additional 10% daily dietary energy to the host (23–25).

Evolution of dietary sugars, sugar substitutes and host metabolism

Advances in food science, chemistry and manufacturing have steered production of sugar sources away from refined cane and beet to cheaper corn-derived sweeteners such as high-fructose corn syrup (HFCS) and developed low-calorie or calorie-free sugar substitutes such as sugar alcohols and artificial sweeteners. An overview of these dietary components and their metabolic capacities is outlined in Table 1.

Fructose and high-fructose corn syrup

Fructose is ingested as one of two sources in our diet; as either free fructose or fructose bound to glucose (i.e. sucrose). Differences in uptake and metabolism of free fructose or fructose consumed as sucrose have been suggested (3,26); however, the magnitude of any differences between consumption of the two forms may be negligible when total fructose consumption (i.e. free fructose plus fructose consumed as sucrose) is considered (3). Fructose as a naturally occurring monosaccharide present in many fruits and vegetables provides only modest amounts of free fructose to the host. Conversely, the soring use of HFCS as sweetener in soft drinks, baked goods and condiments is imparting a new challenge upon the intestinal environment in managing free fructose overloads (27). HFCS is composed of a mixture of free fructose and glucose, typically 55% fructose to 45% glucose; however, these ratios frequently vary (28). Conservative estimates indicate 132–312 kcal $person^{-1}$ d^{-1} is consumed as HFCS in the United States, where its widespread use in food manufacturing prevails compared with Western Europe, representing an increase in free fructose load of 158.5 kcal $person^{-1}$ d^{-1} in 1978 to 228 kcal $person^{-1}$ d^{-1} in 1998 (27,29). Furthermore, per capita estimates in the United States indicate HFCS consumption increased from 56.1 g d^{-1} between 1975 and 1980 to 73.4 g d^{-1} during the 1994–2005 period (30). This substantial increase in fructose consumption has paralleled the increased incidence of obesity in the United States, suggesting its contribution to development of obesity (27,31,32). This assumption remains controversial as others have noted no unequivocal evidence linking free fructose consumption with metabolic disorders (3). The degree to which consumption of free fructose contributes to obesity may, however, be life stage dependent beginning with

Table 1 Absorptive and fermentable sugars, sugar alcohols and artificial sweeteners common to the Western diet

	Classification	Sweetness (vs. sucrose)	Intestinal transport	Maximum ingestible capacity without adverse effects
Fructose	Monosaccharide, hexose	173%	GLUT5 GLUT2	25–50 g suffice for >50% of humans (27).
Glucose	Monosaccharide, hexose	73%	GLUT2 SGLT-1	Absorption consequence free; Rare absorption disorder characterized by mutation in SCL5A1 gene (90).
Sucrose	Disaccharide; fructose-glucose α-1,4-linkage	100%		Absorption of glucose and fructose moieties as noted above; process dependent upon sucrose hydrolysis.
HFCS-55	High fructose corn syrup 55% fructose, 45% glucose		GLUT5 GLUT2	Similar to fructose because of the free fructose load (27).
Erythritol	Monosaccharide, Sugar alcohol	75–80%	Passive diffusion	>50 g d^{-1} (45–47).
Xylitol	Monosaccharide, Sugar alcohol	100%	Passive diffusion	>35 g d^{-1} (45–47).
Sorbitol	Monosaccharide, Sugar alcohol	50–60%	Passive diffusion	>30 g d^{-1} (45–47).
Mannitol	Monosaccharide, Sugar alcohol	80–95%	Passive diffusion	>40 g d^{-1} (45–47).
Lactitol	Disaccharide, Sugar alcohol	30–40%	Passive diffusion	>20 g d^{-1} (45–47).
Sucralose, Saccharin, Aspartame, Acesulfame-K Neotame	Artificial sweetener	100–600%	GLUT2 (sucralose)	Unknown; carcinogenicity and acute toxicity vary (5).
D-Psicose	'Rare sugar', C-3 epimer of D-fructose	70%	Passive diffusion	0.55 g kg^{-1} body weight (1,56)
D-tagatose	Ketohexose structurally similar to fructose	92%	Passive diffusion	>30 g d^{-1} (68).
Stevioside	Glycoside	300%	Low uptake reported	Recommended daily dosage of 25 mg kg^{-1} body weight. Steviol may be carcinogenic (60).

excessive consumption in childhood (33). For example, obese children ingest twice the amount of fructose in the form of sweets and sugar sweetened beverages in comparison to normal-weight children, a trend which if continued into adulthood could have implications for weight status (34,35).

Absorption of free fructose in the small intestine differs markedly from glucose and is primarily mediated by the GLUT5 transporter, with participation of GLUT2 also reported (36). Following food intake, apical GLUT2 and GLUT5 transporters alter their membrane insertion rate and activity in response to β-adrenergic agonists, gut-derived hormones (e.g. glucagon-like peptides 1 and 2 [GLP]) and leptin levels (36–39). Fructose entering portal blood is extracted nearly 100% at first pass by the hepatic GLUT2 transporter where it is oxidized to CO_2 with subsequent conversion to lactate and glucose (3). Lactate and glucose are then directed to *de novo* lipogenesis or converted to glycogen for storage (Table 2) (3,40).

Fructose has been reported as potentially orexigenic when administered centrally to mice, demonstrating an innate disruptive tendency in energy balance regulation (41). Fructose elicits no insulin secretion from β pancreatic cells and fails to stimulate satiety signalling from the brain (38). This effect may be mediated by a lack of functional GLUT5 in the brain despite its observation in various brain cells (42,43). This lack of insulin production results in insufficient plasma leptin levels needed to regulate further food intake (44). Leptin is a pleiotropic hormone produced by many tissues, with serum levels correlating positively with body fat (36,45). Stomach-derived leptin has been demonstrated to regulate butyrate uptake by monocarboxylate transporter MCT-1 and SGLT-1 sodium-dependent glucose transport in the small intestine (46,47). Leptin also imparts a synergistic increase in GLUT5 mRNA expression in rats fed a high-fructose diet, resulting in a positive-feedback loop of continual increased fructose absorption and subsequent leptin secretion (36,48). Furthermore, a concomitant decline in hepatic and intestinal fasting-induced adipocyte factor (Fiaf) by fructose feeding was observed and not ameliorated by leptin administration (36). Fiaf is a circulating inhibitor of lipoprotein lipase, an enzyme promoting triglyceride storage (49). Leptin may further potentiate the lipogenic effect of fructose by induction of SREBP-1c and ACC-1, a hepatic lipogenic transcription factor and regulatory enzyme of fatty acid biosynthesis, respectively (36). Discovery of this intricate network of fructose-mediated leptin secretion, GLUT5 regulation and Fiaf suppression illustrates additional contributory mechanisms of free fructose consumption to lipogenesis with implications for development of hyperlipidemia and metabolic disorders.

Table 2 Host metabolism and potential implications of consuming various dietary sugar compounds

	Host metabolism Potential metabolic health consequences
Fructose/HFCS	Intestinal GLUT5 and / or GLUT2 uptake. Extracted nearly 100% at first passage by the liver. No ATP or citrate feedback inhibition (3).
	De novo hepatic lipogensis; conversion to glucose with subsequent storage as glycogen or released plasma glucose.
Glucose	Intestinal SGLT-1 and GLUT2 uptake (apical) and GLUT2 (basolateral). Hepatic metabolism similar to fructose albeit with insulin regulation (3,54,71).
	Aberrant hepatic glucose and fatty acid results in increased pancreatic insulin production leading to insulin resistance and type II diabetes mellitus.
Sugar alcohols	Absorption in small intestine via passive diffusion and as a result enter the circulation slower than glucose or fructose; absorption dependent upon degree of polymerization (47).
	Confer little to no caloric value by host metabolism; excessive consumption results in laxation and watery stool (4,45).
Artificial sweeteners	No effect when consumed alone. Natural and artificial sweeteners bind to taste receptors, conferring a synergistic effect on downstream target regulation, including GLUT2 up-regulation in the small intestine (54).
	May augment hunger and enhance natural sugar uptake however there is no clear evidence definitely supporting this effect; Effects appear sweetener-dependent (5)
Rare sugar	Absorbed in small intestine and rapidly excreted in urine with no host energy gain. Large intestinal fermentability varies (59,68,78).
	May suppress postprandial blood glucose and insulin via repression of intestinal α-amylase, sucrase and maltase activities (55,57,59). D-tagatose may ameliorate symptoms of type II diabetes by promoting weight loss and improving high-density lipoprotein cholesterol (67).

HFCS, high-fructose corn syrup.

Sugar alcohols

Sugar alcohols are industrially produced replacement sugar sources and are neither sugars nor alcohols, but rather hydrogenated saccharides harbouring a hydroxyl in place of a sugar ketone or aldehyde moiety (50). Sugar alcohols, with the exception of erythritol, are produced by hydrogenation of maltose, lactose, palatinose, glucose, xylose or partially hydrolyzed starch derivatives (5). Sugar alcohols are only partially absorbed from the small intestine with absorption values ranging from 0% for lactitol to 80% for sorbitol (51). Metabolism is also incomplete with 10%–20% of sorbitol and xylitol and 30%–40% of mannitol excreted in urine (52). Neither plasma glucose nor insulin levels are affected by sugar alcohol absorption and metabolism, particularly when monosaccharide forms are consumed. Hydrolysis of disaccharide sugar alcohols into their glucose moieties, however, facilitates host glucose absorption and metabolism (53). ^{14}C-labelled experiments with various sugar alcohols categorized their caloric value at approximately 2 kcal g^{-1} energy, representing 50% of sucrose-derived energy (5). Side effects of sugar alcohol consumption are dose dependent and generally absent up to a specific load (typically expressed as g d^{-1}) after which moderate to severe GI problems such as watery stool, diarrhoea, nausea and borborgymi may arise (Tables 1 and 2).

Artificial sweeteners

Artificial sweeteners are non-nutritive sweeteners which entered the consumer market in the 1950s with the introduction of cyclamate in the United States. Cyclamate was subsequently banned in 1968 because of evidence linking high cyclamate consumption to bladder cancer in rats (54). Since then, artificial sweeteners have gained popularity as a solution in maintaining the palatability of foods while substantially reducing or eliminating caloric content. The U.S. Food and Drug Administration has approved five non-nutritive sweeteners for human use: saccharin, sucralose, aspartame, acesulfame-K and neotame (Table 1). Estimates suggest 15% of people >2 years of age regularly consume artificially sweetened products (4). Effects on hunger promotion, satiety and energy balance elicited by artificial sweeteners have been heavily debated. Initial reports suggested consumption of non-nutritive sugar substitutes promotes hunger by stimulating cephalic phase insulin response, altering volumetric appetite signalling of the stomach in response to changes in osmotic load and empting rate as well as stimulating GLP-1 secretion by taste receptor activation in the small intestine (4,55–58). Gross generalizations on the effects of artificial sweeteners cannot be made as the effects are sweetener dependent. For example, cephalic insulin response has been demonstrated for saccharin but not aspartame and GLP-1 secretion has been unequivocally demonstrated following sucralose ingestion only (4,55,59). Furthermore, augmentation of hunger by non-nutritive sweeteners may not be relevant when ingested as a beverage at mealtime and it is unclear whether heightened hunger directly translates into increased energy consumption (Table 2) (4). Hence, downstream metabolic effects of non-nutritive sweetener consumption remain inconclusive.

Rare sugar

D-Psicose (D-ribo-2-hexulose) is a C-3 epimer of D-fructose and classified as a rare sugar because of its scarce natural abundance. It naturally occurs in wheat, *Itea* plants as well as cane and beet molasses but is more commonly mass produced with isomerase and D-tagatose-3-epimerase (60). D-Psicose is absorbed in the small intestine and rapidly excreted in urine (61). No energy is gained upon D-Psicose ingestion making it an attractive 'natural' sugar substitute (62). Other potential health benefits have been ascribed to its regulation of plasma glucose concentrations via repression of intestinal α-amylase, sucrase and maltase activities during oral carbohydrate tests (Table 2) (63). Suppression of postprandial blood glucose and insulin levels during administration of >5 g D-Psicose suggests this sugar may be attractive for developing 'naturally' sweetened, diabetic-friendly food products (60,64).

D-tagatose represents another ketohexose with structural similarity to fructose but which is commonly produced from microbially driven bioconversion of D-galactose (65). D-tagatose is prized for its sweet taste and bulking properties but apparent low energy status. Recent studies have heralded D-tagatose in type II diabetes management because of weight loss and improved high-density lipoprotein cholesterol in subjects administered by D-tagatose daily as well as in mice supplemented by a D-tagatose diet (66,67). Mammalian metabolism of D-tagatose has been attributed to several different mechanisms including passive diffusion either via the fructose transporter or other sugar transport system, facilitating absorption of up to 81% of 15 g orally administered (68). Stevioside is the main sweet component in the leaves of *Stevia rebaudiana* and is naturally occurring sweetener with effects similar to artificially-derived sweeteners, with its sweetness approximately 300× greater than sucrose (69). Steviolbioside and rebaudioside are other occurring sweet components extracted from the Stevia plant, however, in low abundance. Stevioside and rebaudioside were recently approved for use in the European Union despite being regarded as safe for consumption in Asia and North America for many years.

Microbial species capable of fructose, sugar alcohol and artificial sweetener metabolism

Comparably little information exists on human gut-associated microbial species bestowed with fructose, sugar alcohol and artificial sweetener metabolic machinery. Despite the limited information available, an overview of species involved in fructose and sugar substitute metabolism is summarized below and outlined in Table 3. Lactic acid bacteria (LAB), particularly the lactobacilli, represent the best characterized group of fructophilic microbes (70,71), although this activity has also been reported in the *Clostridium* cluster IV genus *Faecalibacterium*. LAB and γ-Proteobacteria are the predominating organisms involved in sugar alcohol metabolism (72). Sorbitol and mannitol fermentation by *Escherichia coli*, *Salmonella* spp., *Shigella* spp., as well as *Lactobacillus* spp. and *Streptococcus* spp. was in fact reported as early as the 1930s (73). Sorbitol metabolism has also been observed by species of *Selenomonas ruminantium* in sheep rumen, suggesting this metabolic capacity may be widely distributed among microbes (74). Xylitol is generally regarded as beneficial in preventing oral lactobacilli, streptococci and actinomycetes growth; however, less is known about microbially mediated intestinal fermentation (75).

Table 3 Human gut-associated microbial species capable of metabolizing fructose, sugar alcohols, artificial sweeteners and rare sugars

Compound	Microbial species	Reference
Fructose	Lactic acid bacteria. *Lactobacillus*, *Bifidobacterium*, *Faecalibacterium*	(61–63)
Sorbitol	*E. coli*, *Salmonella*, *Shigella*	(64,65)
Mannitol	*Lactobacillus*, *Streptococcus*	
Xylitol	Generally unfavourable for microbial metabolism; Metabolism by some *Streptococcus mutans* sp.	(66)
Artificial sweetener: aspartame	*Streptococcus mutans*	(68–70)
Stevioside	*Bacteroides*	(67)
D-Psicose	*Bacteroides*, *Bifidobacterium*, *Ruminococcus*	(56)
D-Tagatose	*Enterococcus, Lactobacillus*; Lactic acid bacteria	(77)

Stevioside metabolism by human colonic microflora is mediated predominately by *Bacteroides* with steviol the major metabolite (76). Investigation of D-psicose fermentation by 35 microbiota representatives also identified a *Bacteroides*-dominance, suggesting 'rare' sugars may be metabolized by the sus carbohydrate operon (8). *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bifidobacterium dentium* and *Ruminococcus productus* were all identified as capable D-Psicose metabolizing species (61). Human intestinal bacteria related to *Enterococcus* and *Lactobacillus* as well as common genera of LAB are capable of D-tagatose fermentation (77). Furthermore, ileal, cecal and large intestinal microbial populations in swine readily metabolize D-tagatose to H_2, methane and SCFA (78). Conversely, saccharin metabolism has been reported to increase the relative amount of aerobic intestinal bacteria and reduce *Proteus vulgaris*-dependent ammonia production (79). Saccharin, acesulfame K, cyclamate uptake and utilization by *Streptococcus mutans* have

also been reported, a process capable of impairing microbial glucose metabolism (80,81).

Sugar metabolism, malabsorption and the gut microbiota

Modern science has endowed us with many natural and synthetic sucrose replacements that continue to receive both praise and scrutiny for weight management during this global girth expansion. Despite a reduced or absent caloric contribution of sugar alcohols and rare sugars to the host energy balance, unabsorbed substrate ultimately passes to the large intestine where it becomes fermentable substrate for the gut microbiota (Tables 1 and 2) (5,61). Fructose may serve as both a direct energy source and potent downstream metabolic effector; however, fructose is also one of the most poorly absorbed short-chained carbohydrates with 50 g free fructose capable of inducing malabsorption in 80% of people (Tables 1 and 2) (82–84). Fructose malabsorption is clinically defined by breath excretion analyses of H_2 resulting from microbial fructose fermentation (82), demonstrating an inherent genetic propensity of the gut microbiota to utilize dietary fructose sources. Artificial sweetener fermentation by gut microbiota remains either unexplored or poorly documented, but its capacity is logically extrapolated based on the fermentability of these other sugar compounds in the large intestine.

Fructose and sugar substitute-dependent conditioning of the commensal gut microbiota

In light of the increased consumption of fructose, sugar alcohols and artificial sweeteners as both probable cause and consequence of the obesity epidemic, the impact these compounds are potentially exerting upon our resident commensal flora may be profound. Consequently, the contribution of gut microbial metabolism of unabsorbed or malabsorbed sugar substrate must be considered additive to host metabolism, yet neither concept has been extensively investigated in humans. The reduced diversity in our fructose- and sugar substitute-laden, plant polysaccharide-poor Western diets may be conferring substantial evolutionary pressure on the gut microbiota. On one hand, the microbiota must adapt to 'unfamiliar' substrates such as sugar alcohols and artificial sweeteners, and on the other they are confronted with excessive loads of 'familiar' substrate such as fructose. Adaptive metabolism has been demonstrated for D-tagatose fermentation in rat and swine models and much of the undesired effects of excessive sugar alcohol consumption are ascribed to bacterial production of H_2, CH_4 and CO_2 during fermentation (5,50,78). As a result, both the microbiota composition and metabolic activities are subject to extensive modification during substrate conditioning. The concept of dietary modulation is not new but has generally been consciously exploited to achieve health benefits. For example, resistant starch is a prominent substrate for butyrate-producing bacteria related to *Roseburia/Eubacterium rectale* as well as *Ruminococcaceae* (85). Inulin and fructooligosaccharides are prebiotics used to stimulate Bifidobacteria, resulting in liberation of lactate and other oligosaccharides, forming a well-characterized metabolic cross-feeding pathway with butyrate-producing *Firmicutes* (86,87).

Analogous to conscious modulation of the gut microbiota by inclusion of beneficial dietary components, exclusion of substrate by a limited diet may produce the reverse effect, resulting in a loss in diversity. While the increased Firmicutes : Bacteroidetes ratio relationship to obesity remains heavily debated, the concept of obesity associated with reduced bacterial diversity and altered gene and metabolic pathway expression is commonly agreed upon (13,16,88). Supporting this hypothesis is the identification of a Western-diet associated gut microbiome enriched in genes encoding pathways related to the phosphotransferase system, fructose and mannose metabolism, and glycolysis/gluconeogenesis, but depleted of genes required for starch and sucrose metabolism (88). This microbiome was associated with a bloom in an uncultured clade within the Firmicutes class Mollicutes, suggesting that a Western diet may indeed be preferred by Firmicutes with potential detrimental effects on Bacteroidetes survival. *Bacteroides* are the most prominent Bacteroidetes genus and are equipped with an extensive array of polysaccharide and glycan utilization machinery, demonstrating their preference for diets containing complex plant material (8,89). *Bacteroides* reside near the top of the metabolic cross-feeding hierarchy, providing substrate for those species reliant upon polysaccharide hydrolysis products for survival. A loss or reduction in *Bacteroides* as a consequence of Western diet substrate conditioning might ultimately result in dysbiosis and loss of several microbe-specific niches in the gut, contributing to differences observed in obese and normal-weight microbial phylogenies (13,33).

Increased dietary energy extraction and metabolism may promote metabolic disorders

The concept of more efficient dietary energy extraction by obese microbiota was initially demonstrated in a leptin-deficient *ob/ob* mouse model of obesity and later observed in obese adults as well as children (15,16,33). While the amount of ingested substrate ultimately determines the extractable energy content, both fructose and sugar substitute metabolism could also enhance this process. Substrate conditioning with excessive fructose loads or genetic evolution of the gut microbiome as survival mechanism to increased exposure to 'unfamiliar' sugar substrates could result in acquisition of additional metabolic power.

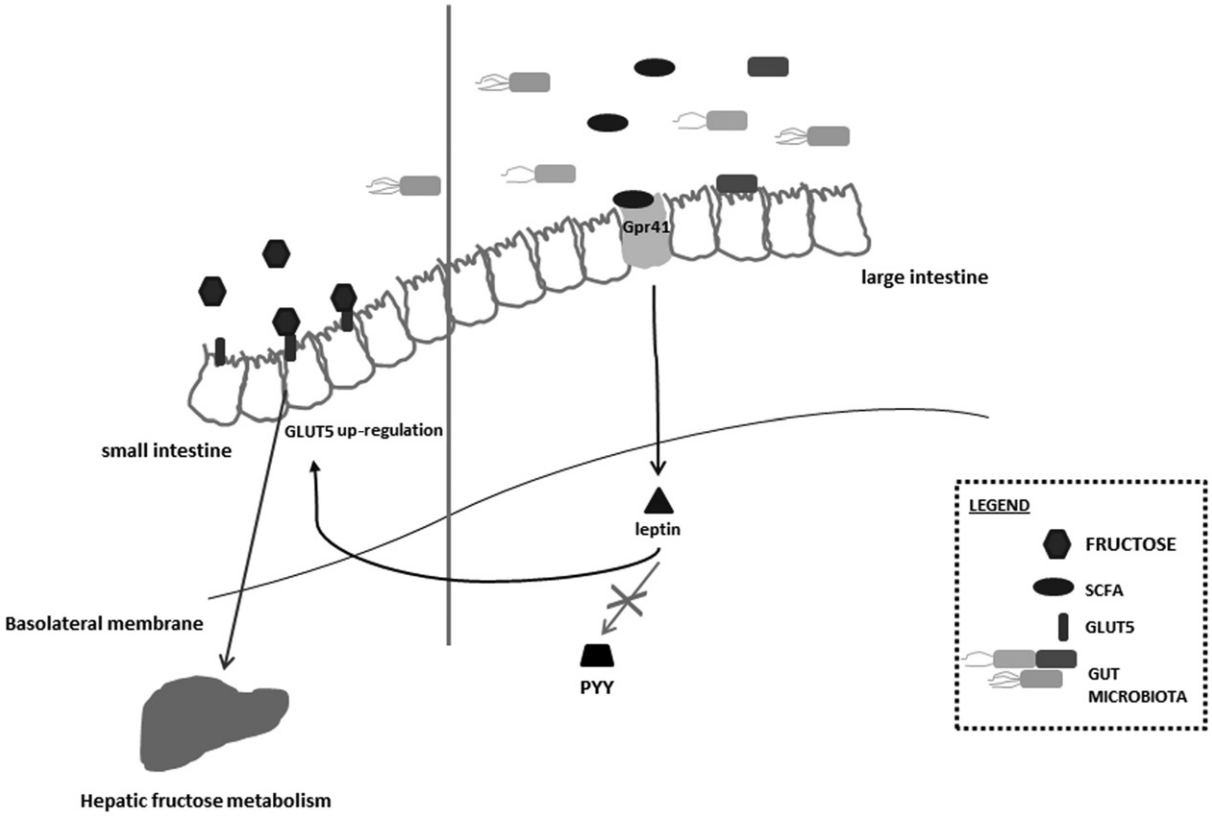

Figure 1 Proposed positive-feedback loop of leptin-regulated host–microbe fructose uptake and metabolism.
Gpr41, G-protein coupled receptor 41.
Hypothesis: Excessive dietary fructose intakes resulting in malabsorption and passage to the large intestine result in microbial fermentation to short-chain fatty acid (SCFA). Gpr41 intestinal epithelia receptors sense increased microbial activity and metabolism in the inner mucus layer by enhanced Gpr41 binding of SCFA. Gpr41-SCFA binding activates leptin secretion which inhibits PYY activity, resulting in slowed gut transit rates. Slowed gut motility allows more undigested carbohydrate to reach the large intestine, further promoting increased microbial metabolism and leptin secretion. Leptin may directly up-regulate GLUT5 fructose transporter expression and insertion into the epithelium which may enhance host fructose uptake. Fructose subsequently exits the GLUT2 basolateral membrane transporter, entering the portal circulation where it is extracted nearly 100% by the liver and converted to lactate, glucose or fatty acids.

Increased metabolic processes yielding more SCFA could provide the host with additional glucose generated by intestinal SCFA uptake and conversion via the Krebs cycle. This process is well documented in ruminants for propionate; however, much less is known about the contribution of SCFA on glucose production in humans (90,91).

SCFA resulting from exhaustive substrate utilization may have additional consequences for the host. Many authors propose increasing SCFA production as obesity treatment because of the reported ability of propionate and acetate to reduce plasma and hepatic fatty acid content, lower cholesterol and potentially improve insulin sensitivity (91,92). Butyrate is regarded as beneficial because of its anticancer properties related to epithelial cell-cycle regulation as a histone deacetylase inhibitor (93). Nevertheless, many of the demonstrated beneficial effects of SCFA are inconclusive in humans, as e.g. the effect of propionate on hypocholesterolemia (94). SCFAs are also pleiotropic ligands for G protein-coupled receptors Gpr41 and Gpr43 expressed in the distal small intestine and colon (95–97). Recent evidence suggests SCFA may promote GLP-1 secretion from Gpr41- and Gpr43-expressing L-cells with implications for improved glucose tolerance (96). This effect may, however, be SCFA specific, demonstrated by elevated GLP-1 blood concentrations following rectal acetate administration (97). Conversely, signal transduction of SCFA bound to Gpr41 stimulates leptin expression and enhances the appetite, resulting in increased adiposity compared with Gpr41 -/- mice (7). Furthermore, description of Gpr43-mediating propionate and acetate-dependent inflammatory responses involving neutrophil activation contradicts earlier reports of SCFA as anti-inflammatory (98,99).

Emergence of this rather muddled host–microbe interaction picture centred around SCFA production from exhaustive dietary energy extraction suggests current dietary trends may be exacerbating obesity and metabolic

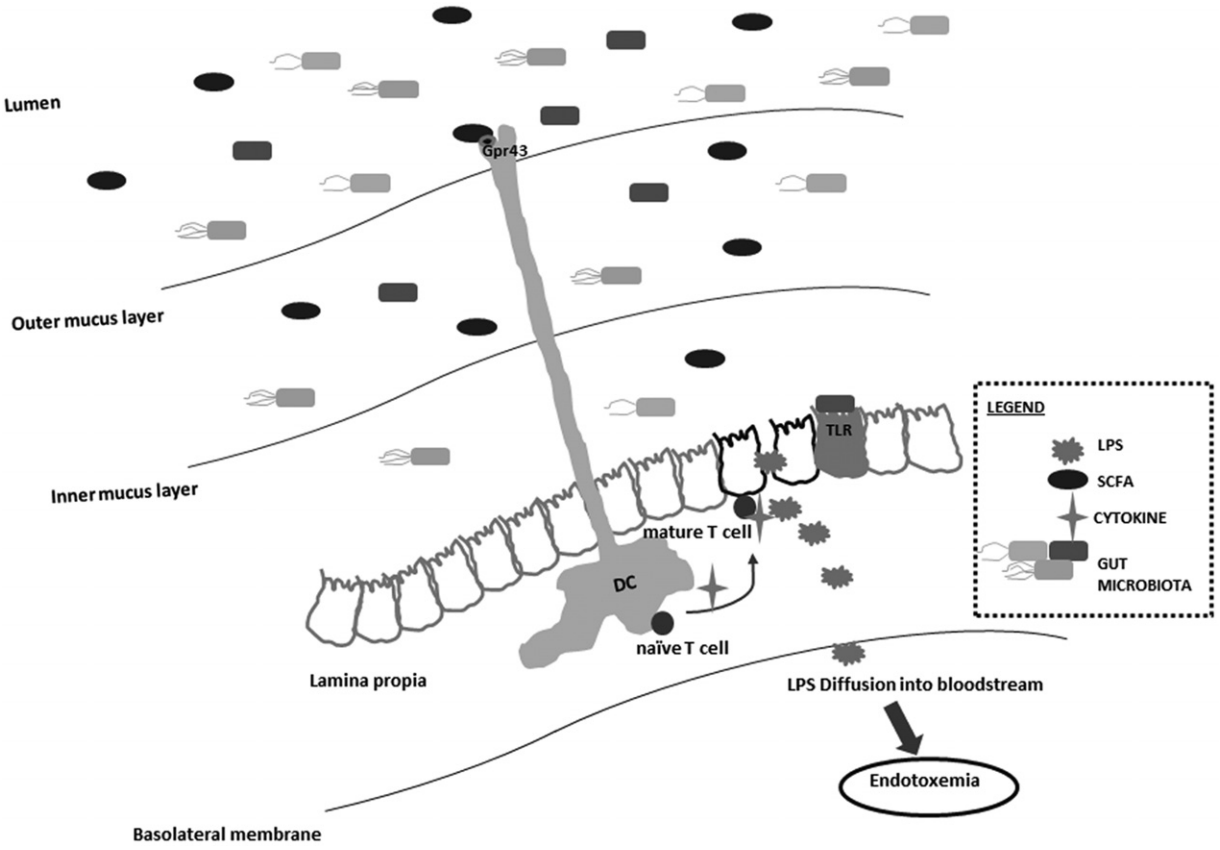

Figure 2 Proposed mechanism of fructose and sugar substitute dietary intakes promoting intestinal inflammation and endotoxemia. DC, dendritic cell; Gpr43, G-protein coupled receptor 43; dark-shaded cell; host-microbe communication via TLR; LPS, lipopolysaccharide; TLR, toll-like receptor.
Hypothesis: Enhanced dietary energy extraction from increased fructose and/or sugar substitute loads results in increased microbial metabolic activity and short-chain fatty acid (SCFA) production. DC continuously sampling luminal and mucus-associated microbial metabolism by Gpr43-mediated SCFA detection bind naïve T cells, releasing cytokines necessary for T cell maturation. Innate and adaptive pro-inflammatory immune responses decrease intestinal epithelial tight junction integrity (black outlined cells) allowing LPS to breach the intestinal barrier and exit the basolateral membrane. LPS entering the systemic circulation may promote obesity-associated endotoxemia (adapted from Van den Abbeele *et al.* (100)).

disorders. The gut can no longer be considered a simple black box, whose processes are spatially restricted as signals emerging from host–microbe interactions along the GI tract are systemically communicated along the gut-brain axis. Regulation of satiety and energy balance may be disrupted by Gpr41-SCFA-bound stimulation of leptin secretion and concomitant repression of the gut motility regulator, PYY (7). This interaction could promote a positive-feedback loop whereby slowed gut transit times promote exhaustive fermentation of unabsorbed or malabsorbed fructose and sugar substitutes, enhance small intestinal energy extraction by Gpr41-dependent leptin up-regulation of the GLUT5 fructose transporter and induce lipogenesis by leptin-dependent repression of Fiaf (Fig. 1). Evidence also exists for Gpr43 participation in the innate immune response as its expression is closely regulated with Toll-like receptor (TLR) TLR2 and TLR4 expression (98). SCFA induction of epithelial Gpr43 may represent a mechanism for sensing microbial activity within the adherent mucus layer where microbes are in direct contact with the epithelium and may be an important mediator of commensal tolerance (98,100). Furthermore, metabolic activity in the lumen may be sampled by extension of Gpr43-expressing dendritic cells between epithelial tight junctions, promoting possible cytokine-dependent T cell maturation (Fig. 2) (100). Hence, increased microbial activity could promote intestinal inflammation and compromised epithelial integrity, allowing for passage of lipopolysaccharide and other inflammatory stimuli into the systemic circulation, contributing to obesity-associated endotoxemia (8,101).

Conclusion

Identification of a single definitive cause or consequence of the commensal flora to obesity is unreasonable to assume. The multitude of host–microbe interactions elucidated over

the past 5 years provides strong evidence of a multifactorial network of parameters leading to development of obesity and associated metabolic disorders. It is widely accepted that dietary modulation of the gut microbiota is attainable, even desired for promoting certain 'beneficial' health effects. Conversely, the evidence presented here suggests we are unconsciously promoting a 'westernized' conditioning of the gut microbiota to reduced dietary diversity marked by increased consumption of fructose and sugar substitutes. The contribution of increased dietary fat to this process cannot be ignored but is not the focus of this review, having received sufficient attention elsewhere.

Continuous exposure to fructose and sugar substitutes may cause dysbiosis with loss of microbial genetic and phylogenic diversity, promoting evolution and maintenance of a Western gut microbiome. In turn adaptive metabolism generates additional energy sources for the host, which may facilitate aberrant host–microbe interactions leading to perturbed energy regulation and altered gut transit times with subsequent enhancement of dietary energy extraction. These differences in microbial composition and metabolic activity may ultimately be sensed by the innate and adaptive immune system leading to intestinal inflammation with later manifestation as endotoxemia. The combination of these processes can undoubtedly contribute to development of many metabolic disorders associated with obesity. In conclusion, we suggest obesity treatment and prevention could be effectively achieved by promoting intestinal homeostasis through reintroduction of a balanced and diverse diet.

Conflict of interest statement

The authors report no conflicts of interest.

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