The Effect of High-Fat Diet-Induced Pathophysiological Changes in the Gut on Obesity: What Should be the Ideal Treatment?

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Obesity is a metabolic disorder and fundamental cause of other fatal diseases including atherosclerosis and cancer. One of the main factor that contributes to the development of obesity is high-fat (HF) consumption. Lipid ingestion will initiate from the gut feedback mechanisms to regulate glucose and lipid metabolisms. But these lipid-sensing pathways are impaired in HF-induced insulin resistance, resulting in hyperglycemia. Besides that, duodenal lipid activates mucosal mast cells, leading to the disruption of the intestinal tight junction. Lipopolysaccharide that is co-transited with dietary fat postprandially, promotes the release of cytokines and the development of metabolic syndrome. HF-diet also alters microbiota composition and enhances fat storage. Although gut is protected by immune system and contains high level of antioxidants, obesity developed presumably when this protective mechanism is compromised by the presence of excessive fat. Several therapeutic approaches targeting different pathways have been proposed. There may be no one single most effective treatment, but all aimed to prevent obesity. This review will elaborate on the physiological and molecular changes in the gut that lead to obesity, and will provide a summary of potential treatments to manage these pathophysiological changes.

OVERVIEW

The increased prevalence of obesity and obesity-associated complications continues to be a major global health issue. This is due mainly to the cause of obesity that is multifactorial. High-fat (HF), caloric-dense diets, sedentary lifestyles, increased urbanization and psychosocial stress are the most common contributing factors.[1] Obesity itself predisposes one to other diseases such as type 2 diabetes mellitus, hypertension, dyslipidemia, metabolic syndrome (MetS), atherosclerosis, degenerative joint disorders and cancer.[2] The prevalence of MetS increases with the severity of obesity and reaches 50% in morbidly obese youngsters.[3] Effective treatment with better prognosis can be achieved if we have a comprehensive understanding of the pathogenesis of the metabolic disorder. Most studies so far focus on relating aberrant gene expression in the liver and adipose tissues to obesity, while less correlation is made between pathophysiological changes in the gut and obesity. In actual fact, emerging evidence have suggested that intestinal inflammation occurs during the development of obesity.

Inflammation in obese patients corresponds with increased plasma levels of C-reactive protein, tumor necrosis factor (TNF)-α, interleukin (IL)-6, monocyte chemotactic protein-1, IL-8, leptin and osteopontin.[4] Suggested by Spagnuolo et al.,[5] a significant positive correlation between body mass index Z-score and C-reactive protein may lead to obesity-related complications. Obesity and diabetes alter the glucose-stimulated gut-to-hypothalamic nitric oxide signaling pathway. The disrupted enteric glucose detection is associated with a significant increase in inflammatory, oxidative/nitric oxide and endoplasmic reticulum stress gene expression.[6] Signaling mechanisms reported to promote inflammation have also been found to be initiated and/or mediated by luminal lipid and gut microbiota. These observations have collectively suggested the importance of preserving gut function, and a greater understanding of the pathological state of the gut may be useful in finding new strategy to treat and to prevent obesity.

The review will first present different mechanisms in the gut that promote directly or mediate the development of obesity under the influence of HF-diet. These include descriptions of a number of established and hypothetical gut lipid-sensing systems that are present in the body to regulate glucose production. This is followed by addressing the impact of lipid-induced inflammation, and reporting data that linked these pathological changes to obesity. The review will then discuss the role of microbiota, which has been associated with inflammation-driven insulin resistance. Finally, the importance of gut antioxidants will be highlighted. This topic is of particular interest because the presence of antioxidants in the gut appears to be less appreciated compared with its other physiological functions such as metabolism and absorption.

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The second part of this review will summarize potential treatments proposed to manage these pathophysiological changes, namely to point out the effectiveness and feasibility of these therapies, and the use of dietary antioxidants as a probable direction for future treatment.

GUT LIPID-SENSING SYSTEMS

This section aimed to provide evidence about the presence of several lipid-sensing systems in the body, which has been linked to obesity and MetS development. Among the different types of stimulus, cholecystokinin (CCK) is the most established peptide hormone that initiates a gut–brain–liver neuronal mechanism. Lipids in the lumen stimulate the release of CCK from I cells that line the mucosa of the duodenum,[7] which then binds to CCK-A receptor in the gastrointestinal system.[8] The impact of CCK release was demonstrated in an *in vivo* experiment using CCK-8, which is an active form of CCK. By cannulating the gut and using pancreatic clamp techniques, intraduodenally administered CCK-8 reduces hepatic glucose production. The effect was reversed when CCK-A receptor inhibitor MK-329 was co-administered with CCK-8. The importance of CCK-A receptor in regulating glucose production is further evidenced when receptor-deficient rats become glucose intolerant, obese and eventually diabetic. The neuronal network involving CCK is the most well studied. Briefly, hepatic vagotomy, inhibition of gut vagal afferent neurons by anesthetic tetracaine administered into the duodenum, and inhibition of glutamatergic neurotransmission in the nucleus of the solitary tract by direct infusion of *N*-methyl-D-aspartate receptor inhibitor MK-801 have all been shown to negate the ability of CCK-8 to lower glucose production. Clearly, the nucleus of the solitary tract is relaying a signal from the intestine to the liver for the effect on glucose production. Stimulation of this network is independent of changes in food intake, but a mere 3 days of HF feeding attenuates this lipid-sensing mechanism.[9]

Besides CCK, lipid was suggested to induce the production of oleoylethanolamide (OEA) in the mucosal layer of the duodenum and jejunum. OEA is then taken up by CD36, a membrane glycoprotein, which may act both as a receptor and a transporter. OEA within the enterocytes activates peroxisome proliferator-activated receptor-α and promotes satiety.[10] It is reported recently that lipid-induced OEA mobilization in the gut is controlled by sympathetic nervous system. Surgical removal of the sympathetic innervation and pharmacological blockade of β_2-adrenergic receptor abolish the effect of OEA.[11] Taken together, if this hypothetical model is correct, OEA is hence an endogenous proliferator-activated receptor-α ligand where its synthesis can be modulated by pharmacological intervention. The effect of HF on this mechanism has not been demonstrated but HF alone is known to suppress proliferator-activated receptor-α.

In another study, when lipids are infused into the duodenal segment, the elevated long-chain fatty acyl-coenzyme A (LCFA-CoA) inhibits hepatic glucose production. With gut and hepatic vagotomy diminishing this effect[12] support the existence of another gut–brain–liver sensing system. Carnitine palmitoyltransferase-1 (CPT1), located in the outer mitochondrial membrane, is regulating entry of LCFA-CoA into the organelle, where LCFA-CoA undergoes β-oxidation. However, upregulation of intestinal CPT1 as a result of HF feeding[13] may not be helpful because the signaling effect of LCFA-CoA is disrupted in HF-diet-induced insulin-resistant and obese rodents.[12] As for CPT1 expressed in the hypothalamus, an inhibition on the enzyme decreases food intake and glucose production.[14] Nonetheless, the link between intestinal LCFA-CoA and hypothalamic CPT1 in the regulation of glucose homeostasis is currently unclear.

N-acylphosphatidylethanolamine (NAPE) is a class of phospholipids readily synthesized by small intestinal tissues when lipid is consumed. Circulatory NAPE at physiological doses reduces food intake in a dose-dependent manner.[15] Via the method of radioactive labeling, NAPE was found capable of entering the central nervous system and accumulated in the hypothalamus. NAPE acts through the central nervous system because its hypophagia effect was observed in vagotomized rats.[15] In the intestine, NAPE is hydrolyzed to *N*-acylethanolamines by enzyme NAPE-specific phospholipase D. However, animals fed with HF-diet containing variable percentages of fat have *N*-acylethanolamines decrease in a dose- and time-dependent manner.[16] Similarly, chronic HF feeding significantly reduces postprandial NAPE secretion.[15] In short, HF-diet attenuates the secretion of NAPE and *N*-acylethanolamines, which are supposed to be a feedback response to the presence of intestinal lipid.

Different from other sensing molecules, which are lipids, acyl CoA-monoacylglycerol acyltransferase-2 (MGAT2) is an interesting enzyme that controls obesity development. This enzyme catalyzes the conversion of fatty acyl CoA and monoacylglycerol to diacylglycerol. It is highly expressed in the proximal region of the small intestine, and is responsible for about 75% of triacylglycerol synthesis in the intestine.[17] Chronic feeding with HF-diet increases intestinal expression of MGAT2. Conversely, MGAT2-deficient mice are protected from obesity, hyperinsulinemia, glucose intolerance, hypercholesterolemia and hepatic steatosis.[13] Although the underlying mechanism leading to these effects are poorly understood, specific identification of this enzyme with its relevance to MetS parameter is an important finding for obesity treatment.

In summary, sufficient data have demonstrated that central nervous system bridges the function of two visceral organs in the regulation of blood glucose level. Despite the fact that extrapolating these animal data to human condition is not straightforward, it is only through animal study that one can understand the mechanisms involved and identify important targets for the development of more effective therapies for obesity. The presence of multiple gut–brain–liver mechanisms shows the complexity of the lipid-sensing system, which may have potentially increased the difficulty of managing obesity and obesity-related complications.

LUMINAL LIPID AND INFLAMMATION

Gastrointestinal tract (GIT) is the most common route of food and drug administration, which means GIT is generally the first organ to be exposed to attacks by pro-oxidants from the diet,[18–27] phagocytes activated by diet-derived bacteria and toxins,[28] and the effects of HF-diet. All these factors cause

inflammation. HF-diet in particular, is reported to activate mast cells and Toll-like receptors (TLRs).

In BALB/c mice, an *in situ* duodenal administration of butter rich in saturated fat has markedly increased the production of TNF-α by lamina proprial macrophages. TNF-α enhances lymphocyte adherence to microvessels of the mucosa.[29] Cytokine at low level is beneficial as it modulates barrier functions and protects the epithelial layer. However, various LCFAs micelles (range between 10 and 50 μM) administered to lymphocytes (200 μl, 4×10^5 per well) have dose-dependently inhibited the production of interferon-γ.[30] Incubation of LCFAs (0.01 to 0.1 mM) with epithelial cells increases the secretion of growth-regulated oncogene/cytokine-induced neutrophil chemoattractant-1 and IL-6,[31] also in a dose-dependent manner. This means that LCFAs correlate positively with cytokine production, thereby onset of inflammation.

Intraduodenal infusion of polyunsaturated fatty acid-rich lipid emulsion activates intestinal mucosal mast cells, causing the release of histamine, rat mast cell protease-II and prostaglandin D$_2$.[32] The physiological significance of the activation of mast cells during fat absorption is not known. It is possible that by increasing lymph flow and vascular permeability, histamine facilitates the passage of chylomicrons particles through the lamina propria.[32] Rat mast cell protease-II may increase epithelial permeability by suppressing the expression of tight junction-associated proteins zonula occludens-1 and occludin.[33] Moreover, rat mast cell protease-II is specific for mucosal mast cells and selectively attacks type IV collagen in the basement membranes.[34] Of note, an interrupted tight junction has been observed in obesity.[35]

Bacterial endotoxin or lipopolysaccharide (LPS) is present in large quantity in the gut. It is hypothesized by Erridge *et al.*[36] that a small amount of LPS may co-transit with dietary fat from the gut postprandially, and activates leukocyte and endothelial cells. Subcutaneous LPS infusion induces several features of MetS in mice and triggers the release of inflammatory factors.[37] In addition, obese-prone rats treated with HF-diet exhibit an upregulation of TLR4 in the gut wall and a decrease in the intestinal alkaline phosphatase activity.[35] The intestinal alkaline phosphatase is a duodenal brush-border enzyme that detoxifies LPS.[38] Binding of LPS[39] and non-esterified free fatty acids[40] to TLR4 initiates the secretion of various pro-inflammatory cytokines from the macrophages, adipocytes and liver. Conversely, TLR4-deficient mice are partially protected from non-esterified free fatty acid-induced insulin resistance.[40] Similarly, CD14 mutant mice challenged with a HF-diet or given an LPS treatment, resisted cytokine production, hypertriglyceridemia, insulin resistance, obesity and visceral adiposity.[37] With CD14 being a co-receptor of TLR4 suggests the presence of two binding sites on this receptor complex that controls insulin sensitivity as well as the development of MetS parameters.

Overall, luminal lipid by direct action on the enterocytes and through activation of mast cells, causes the release of cytokines. There is sufficient evidence to show that lipid induces inflammation in the course of obesity development. Further to this, Ding *et al.*[41] are convinced that intestinal inflammation precedes and correlates with diet-induced obesity, adiposity and insulin resistance. They suggest that HF interact with gut microbiota to trigger the expression of TNF-α and nuclear factor-kappaB. The absence of microbiota in germ-free (GF) mice has blunted upregulation of these biomarkers, which are primary indicators of inflammation. With regard to this, our understanding on the onset of inflammation is not complete without mentioning the role and the effect of gut microbiota.

GUT MICROBIOTA

Already been reported almost a decade ago that although food consumption was significantly lesser, conventionally raised specific-pathogen free (CONV) mice have a 40% higher total body fat content than the GF mice. Interestingly, GF mice developed a 60% increase in their total body fat when being colonized with microbiota harvested from the cecums of CONV mice.[42] The resistance of GF mice to diet-induced obesity is due mainly to the animal having a different genetic make up for lipid processing in the intestine.

Microbiota via carbohydrate response element-binding protein enhances uptake of monosaccharides and hepatic triglycerides production. Through the suppression of angiopoietin-like protein 4 (Fiaf), which is a lipoprotein lipase inhibitor, microbiota promotes incorporation of triglycerides into the adipocytes.[42] On the contrary, Fiaf is highly expressed in GF mice. Fiaf induces peroxisomal proliferator-activated receptor coactivator-1α in the gastrocnemius muscle whereby this nuclear receptor increases mitochondrial fatty acid oxidation.[43] High levels of phosphorylated AMP-activated protein kinase in GF mice also promote fatty acid oxidation in the skeletal muscle and insulin sensitivity.[43]

Furthermore, microbiota increases energy and lipid metabolism by upregulating genes involved in the tricarboxylic acid cycle and pyruvate metabolism in the liver.[44] By acting via G protein-coupled receptor 41 (Gpr41), microbiota increases adiposity and leptin production. Gpr41-deficient mice demonstrate a decrease in peptide YY (PYY) secretion, and reductions in intestinal absorption and delivery of short-chain fatty acids, as well as hepatic lipogenesis.[44] Including Gpr41, several other Gpr expressed on enteroendocrine cells have been identified as fat sensor that mediates the secretion of GI peptides. Activation of Gpr41 and Gpr43 by short-chain fatty acids leads to the release of PYY,[45] whereas Gpr40[46] and Gpr120[47] via LCFA as ligand of these receptors, have been implicated in CCK release. Although these recent data shed light on the mechanism responsible for gut hormone release, precise mechanisms by which fat is sensed, and subsequent signaling pathways that lead to changes in GI function, energy intake, hence body weight, are still not well understood.

Microbiota is shaped by an innate immune system that helps to defend the host against infection by pathogenic microbes. TLR5, a component of the system and a trans-membrane protein, is highly expressed on the intestinal mucosa. TLR5-deficient (T5KO) mice have significantly higher body masses than age-matched wild-type mice, exhibited sign of hyperphagia, have high production of pro-inflammatory cytokines in the adipose tissue, and developed other hallmark features of MetS. A broad-spectrum of

antibiotics introduced to T5KO mice at the time of weaning for a period of 12 weeks, attenuated HF-diet-exaggerated MetS development. When T5KO microbiota is transplanted into the intestine of wild-type GF mice, the latter developed T5KO MetS phenotype.[48] These data indicate that a change in microbiota composition increases the risk of metabolic disorder.

Recently, Serino *et al.*[49] reported that metabolic adaptation to HF-diet is associated with a change in metabolic phenotype-specific gut microbiota, which is independent of genetic factor and diet. Effects exerted by this signature microbiota, such as increased production of adipokine, adipose cell size and stroma vascular fraction cell number, are facilitated by increased paracellular permeability in the ileum and cecum of the HF-fed mice. There has also been suggestion that microbiota activates vagal sensory neurons and satiety center. However, data describing the effect of microbiota-brain axis on feeding behavior is still lacking,[50] thus will not be discussed in this review. Figure 1 highlights the effects of HF-diet, by which HF through multiple mechanisms, disrupts glucose homeostasis and mediates the development of obesity.

One of the components of the gut that is frequently neglected in most reviews is gut antioxidants. As GIT is the first organ exposed to exogenous compound, microorganism and free radicals, other than the immune system, GIT is expected to possess high levels of endogenous antioxidants, which act to protect itself against free radicals and to filter out pro-oxidants from entering the circulation.[23] With many studies reporting the effectiveness and the use of natural antioxidants to prevent and ameliorate obesity, it might be worthy to better understand and explore the role of gut antioxidants in this context.

GUT ANTIOXIDANTS

Enterochromaffin cells of the mucosal epithelium are the major source of melatonin in the body.[51] The level observed was about 400 times greater than the pineal gland.[52] Melatonin is a powerful antioxidant, a free radical scavenger, and probably the only endogenous gut antioxidant having well-defined properties. Its ability to scavenge a myriad of radical species protects GIT against lipid peroxidation, oxidative DNA and protein damages.[53] Melatonin has anti-aging, anti-carcinogenic and antitumor effects,[54] and it enhances immune function. Majority of these effects is mediated through MT_1 receptor.[55]

Theoretically, gastroduodenal mucosal layer is protected from acid-induced injury by the existing protective mechanism, namely bicarbonate and mucus secreted by the superficial epithelial cells. Intracerebroventricular infusion of the α_1-selective adrenoceptor agonist, phenylephrine, causes significant release of melatonin[56] and bicarbonate[56,57] from the duodenal mucosa. MT_2 inhibition by luzindole (600 nmol/kg, intravenous), blocks bicarbonate[56,58] but not melatonin secretion.[56] This suggests that melatonin-stimulated bicarbonate secretion is mediated via the central nervous system.[56] Melatonin injection (10 mg/kg, intraperitoneal) before physical and psychological stress[59,60] protects the animals from mucosal degeneration, inflammatory cell infiltration and generation of free radicals in the gastrointestinal tissues. Daily injection of melatonin (0.5 mg/kg, subcutaneous) for
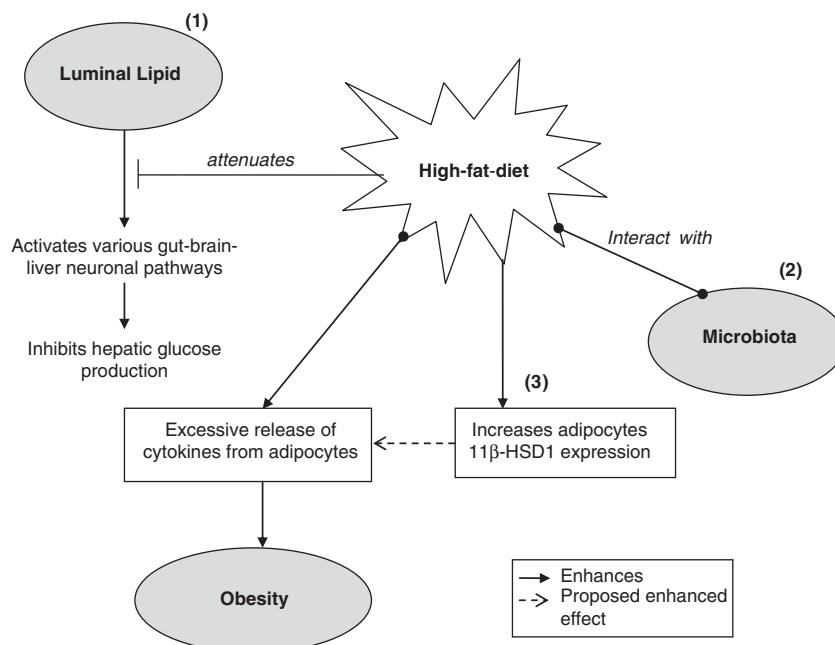

Figure 1 A multipronged mechanism that contributes to obesity development. (1) Luminal lipid activates gut lipid-sensing mechanisms to lower hepatic glucose production and maintain glucose homeostasis. These signaling pathways are suppressed by high-fat (HF) diet. (2) Interaction between microbiota and HF leads to the excessive release of adipocytokines, consequently obesity development. (3) As HF-diet increases 11β-HSD1 expression in the adipose tissues, which in turn promotes visceral obesity, it is likely that 11β-HSD1 enhances the release of adipocytokines, resulting in an effect similar to that observed between HF and microbiota. 11β-HSD1, 11β-hydroxysteroid dehydrogenase-1.

12 days also reverses body weight gain and food intake, which were significantly higher in pinealectomy than sham-operated rats.[61] These favorable outcomes have important impact because psychosocial stress has increasingly been linked to inflammation and obesity.

Apart from melatonin and possibly many other less characterized endogenous antioxidants, gut may gain protection from dietary antioxidants. Flavonoids are the most widely distributed plant antioxidants. They have low bioavailability, with high concentration being observed in the stomach and intestinal lumen.[62–65] The low bioavailability of flavonoids has long been known to be attributed to the compounds hydrophilicity. The glycosylated flavonoids need to be hydrolyzed by bacteria before absorption.[66] Non-flavonoids such as vitamin E and carotenoids, and water-soluble antioxidants are also found at high concentration in the mucosa of the avian species.[67] Flavonoids and other phenolic compounds exert direct protective effects on GIT by scavenging reactive oxygen and the chlorine species.[68]

FUTURE TREATMENT

A wide range of treatments has been proposed to correct pathophysiological changes in the gut as a result of HF consumption. This will be discussed in order following the etiology of the disorder presented above.

There are several approaches to overcome suppression of the gut–brain–liver sensing mechanism. These include upregulation of CCK-A receptor expression, using a CCK-A receptor agonist and modulate signaling proteins that act along the CCK/CCK-A receptor G protein-coupled signaling pathway.[9] With regard to the OEA-mediated local signaling pathway, there have been suggestions to increase the expression of CD36 and magnify OEA, either from diet or through inhibition of OEA degradation.[10] Alternatively, central or intestinal inhibition of CPT1 by genetic and biochemical modification,[14] and increases dietary LCFA-CoA.[12] Other proposals include the use of long-acting NAPE analogs[15] and MGAT2 inhibitor.[13] However, since the concept of lipid-sensing-regulated glucose production is relatively new, more study is required to demonstrate the effectiveness and practicality of these therapies. Study should establish both the toxicity and pharmacokinetics profiles of new drugs that act on the neuronal axis. Other studies such as verification of whether regulating a singular sensing pathway is more ideal or combining pathways will give an additive effect; and comparing the efficacy between established treatments and regulation of lipid-sensing system remained to be explored.

One of the main consequence of HF ingestion is causing significant disruption to the tight junction,[69,70] possibly through activation of mast cells. In this regard, the use of prebiotics and probiotics has some advantages. Prebiotics are mainly non-digestible fibers. They improve the distribution of occludin and zonula occludens-1, and promote normalization of the endocannabinoid system responsiveness in the gut, thereby reduce gut permeability, metabolic endotoxemia and fat mass development.[71] Similarly, probiotics, the live microorganisms, are capable of maintaining epithelial permeability. They avert the re-arrangement of tight junction proteins, upregulate the expression of claudins and occludins, and normalize the barrier function.[72–74] However, both prebiotics and probiotics do not improve metabolic profiles in obese rodents.[75,76] Mast cells stabilizers disodium cromoglycate and ketotifen have been shown to reduce body weight gain and abdominal fat mass in diet-induced obese mice. These animals also have reduced inflammatory cytokines, chemokines and proteases in the serum and white adipose tissues, and have shown better glucose tolerance and insulin sensitivity. Similar observations are found in mast cell-deficient mice fed a Western diet.[77]

There are multiple ways to tackle changes in the composition of microbiota. Bifidobacteria are beneficial to the gut because they reduce intestinal LPS and improve mucosal barrier function.[78] Prebiotics restore the number of bifidobacteria,[79] which was decreased by HF feeding.[78] Young male rats treated for 10 weeks with diets containing 10 and 20% of prebiotic inulin:oligofructose (w/w) had a dose-dependent increase in *Bifidobacterium* spp. and *Lactobacillus* spp.[76] The effects of prebiotics on improving gut barrier function and inflammation are partly through upregulation of GLP2, thus suggesting the potential use of GLP2 to prevent metabolic endotoxemia and metabolic disorders.[80] Co-secretion of GLP1 and GLP2 is implicated to decrease circulatory LPS and cytokines.[71] On the other hand, vancomycin[75] significantly corrects microbiota composition altered in HF-treated animals. The subsequent effects include restoration of intestinal permeability, lowering of plasma LPS, attenuation of adipocyte inflammation and oxidative stress, and improvement in MetS parameters.[81] Despite these therapies, it is necessary to note that the composition of the gut microbiome is dynamic and adaptable. To achieve high efficacy, treatment needs to be specific. This also poses the question of whether targeting microbiota is a realistic approach. There are suggestions that antibiotics affect epithelial integrity, and widespread use of antibiotics in early life may cause obesity.[82] Moreover, as to whether long-term ingestion of a broad spectrum of antibiotics will lead to other disorders is still not known. Hence, it is probably preferable to specifically target on proteins that regulate the development of obesity. For example, Fiaf and proliferator-activated receptor coactivator-1α to modulate fat storage;[42,43] Gpr41 (ref. 44), TLR4, CD14 (refs 37,39) and TLR5 (ref. 48) to prevent low-grade inflammation.

In terms of enzymatic approach, the more established therapeutic target is 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1). This enzyme converts inactive cortisone and 11-dehydrocorticosterone to the active cortisol in human and corticosterone in rats, respectively.[83] In order to understand the mechanism of excessive glucocorticoids-induced growth of visceral fat, Matsuzaki *et al.*[84] conducted an experiment using mice, which overexpress 11β-HSD1 selectively in the adipose tissues. These transgenic mice have increased corticosterone in the adipose tissues, developed visceral obesity and exhibited pronounced symptoms of MetS. There has been intensive research to identify and to produce highly selective 11β-HSD1 inhibitor. Activities include screening of potential compounds from natural resources and synthesizing the inhibitor through computer modeling strategy. A selective and specific reductase inhibitor will prevent side effects[85] and

visceral obesity.[86] On a different note, carbohydrate metabolism has been linked to glucocorticoids formation and modification of 11β-HSD1 activity, whereby targeted inhibition of adipocyte glucose-6-phosphate transport and pentose pathway, reduce 11β-HSD1 activity. In other words, glucocorticoids formation may be controlled by carbohydrate metabolism.[87] Taking this into account, it is probably necessary to simultaneously monitor energy expenditure when developing an 11β-HSD1 inhibitor.

Last but not least, the potential use of dietary antioxidants. The ability of antioxidants to restore and maintain normal gut physiology is receiving much attention lately. As reported by Jurgonski et al.,[88] antioxidants improve glycemia, atherogenic index, antioxidant status and gut function. The authors show that ethanol extract of the chicory seeds containing 9.6% caffeoylquinic acids normalizes the total content of short-chain fatty acids in the cecal digesta, which was decreased in animals receiving high cholesterol and fructose diet. In another study, grape, which is rich in polyphenols, stimulates the proliferation of various species of Lactobacillus. Outcome of the study suggests that plant foods with high dietary fiber and polyphenols content enhance GIT health by promoting a beneficial microbiota profile.[89] Meanwhile, antioxidant resveratrol given to HF-fed mice has helped to re-adjust the level of active GLP1 in the portal vein and intestine back to basal levels. Resveratrol also normalizes HF-diet-induced modification of cecal bacterial composition and decreases the elevated colonic TNF-α.[90] Moreover, because melatonin increases the secretion of mucosa-protecting agents and prevents intestinal inflammation, food rich in serotonin and tryptophan may well be a non-pharmacological treatment to alleviate obesity. Table 1 summarizes treatments that may potentially counteract the effect of HF-diet on gut physiology.

PERSPECTIVES AND CONCLUSIONS

HF diet is one of the main causes of obesity development. Since gut is the first line of absorption, modulating molecular pathways that are activated by luminal lipids is probably a more effective mechanism than targeting other tissues in the body. Studies of the gut–brain–liver neuronal axis have shown that excessive fat impairs the signaling mechanism and hepatic glucose homeostasis. In addition, HF diet increases the release of TNF-α from the gut, alters mucosal immunity, activates mast cells, increases vascular permeability, and disrupts the intestinal basement membranes. Absorption of dietary fat enables uptake of LPS, which further increases the secretion of pro-inflammatory cytokines and intestinal permeability. Gut microbiota have received considerable interest over the last decade, seemingly due to increasing evidence of microbiota regulating fat storage, and are playing a pivotal role in governing obesity development. More important, HF diet promotes inflammation and obesity by interacting with and altering gut microbiota composition.

With reference to studies of gut microbiota, antibiotics are without doubt an obvious and straightforward choice of treatment to restore the altered microbiota profile. However, as the first line of body defense against harmful pathogens, GIT is arguably the largest immune system in our body. Gut is

Table 1 The pathophysiology of gut in obesity development and the proposed treatments for each disorder

Pathophysiology	Treatment options
Impaired gut lipid-sensing systems	To restore pathways by normalizing the specific protein and enzyme expression
Altered microbiota composition	Antibiotics Prebiotics
Disrupted barrier function	Prebiotics Probiotics Antibiotics Mast cells stabilizers
Increased 11β-HSD1	Selective 11β-HSD1 inhibitor Modulate carbohydrate metabolism pathway
Altered microbiota status overrides the effects of gut antioxidants?	*Dietary antioxidants?* Reported to increase: *Lactobacillus* Bifidobacteria Melatonin synthesis? Short-chain fatty acids Glucagon-like peptide-1 Reported effects: Reduce inflammation Preserve mucosal cell integrity Form mucosal protective layer Prevent obesity Reduce appetite Improve glycemia Improve atherogenic index Improve microbiota profile

Abbreviation: 11β-HSD1, 11β-hydroxysteroid dehydrogenase-1.
It was hypothesized that the altered microbiota status has outcompeted the effects of gut antioxidants. With the widespread beneficial effects of antioxidants, increased consumption of dietary antioxidants may be effective to overcome the adversity and to prevent obesity.

also presumably having high levels of endogenous and exogenously acquired antioxidants. These findings collectively indicate the coexistence of intestinal defense mechanisms and microbiota, working in concert in maintaining mucosal homeostasis. Therefore, it is tempting to suggest that one of the reasons for obesity development is the changes in the microbiota composition superceding the protective mechanism that the gut possesses. This may be similar to gastric ulcer that occurs as a result of an imbalance between acid and bicarbonate secretion. Unless the cause of obesity is confounded by genetic factors, dietary antioxidants, which may preserve gut function and restore the anatomical and physiological changes in the gut, might be an area that is worthwhile to explore further. The effectiveness of dietary antioxidants in this context is shown in the recent literature. In addition to their ability to promote the normal physiological function of the gut, dietary antioxidants are expected to be devoid of side effects that may accompany the use of antibiotics.

CONFLICT OF INTEREST

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ☞ There are multiple and distinctive mechanisms in the gut that maintain metabolic homeostasis.
- ☞ Pathophysiological changes in the gut are associated with obesity development.
- ☞ Gut inflammation may be an early sign of obesity.

WHAT IS NEW HERE

- ☞ Treating the gut may be more effective than treating other tissues as a means to control obesity.
- ☞ Maintaining the gut microbiota composition is more beneficial than other approaches in the management of obesity.
- ☞ Dietary antioxidants are an ideal alternative to conventional drugs for obesity treatment.

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