PERSPECTIVE

Obesity and Asthma: Microbiome–Metabolome Interactions

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Abstract

Obesity is a risk factor for asthma, but obese subjects with asthma respond poorly to standard asthma drugs. Obesity also alters gut bacterial community structure. Obesity-related changes in gut bacteria contribute to weight gain and other obesity-related conditions, including insulin resistance and systemic inflammation. Here, we review the rationale for the hypothesis that obesity-related changes in gut bacteria may also play a role in obesity-related asthma. The metabolomes of the liver, serum, urine, and adipose tissue are altered in obesity. Gut bacteria produce a large number of metabolites, which can reach the blood and circulate to other organs, and gut bacteria–derived metabolites have been shown to contribute to disease processes outside the gastrointestinal tract, including cardiovascular disease. Here, we describe the potential roles for two such classes of metabolites in obesity-related asthma: short-chain fatty acids and bile acids. Greater understanding of the role of microbiota in obesity-related asthma could lead to novel microbiota-based treatments for these hard-to-treat patients.

Keywords: airway; immune system; bile acids; short-chain fatty acids

Obesity is a global epidemic. The World Health Organization estimates that, in 2014, more than 0.5 billion adults were obese and another 1.9 billion were overweight. Obesity is a risk factor for type 2 diabetes, hypertension, and atherosclerosis. Obesity has also emerged as a risk factor for asthma. The mechanistic basis for this relationship has yet to be fully elucidated. Here, we describe evidence supporting the hypothesis that obesity-related changes in the gut microbiome may contribute to the etiology of obese asthma.

Obesity and Asthma

Obesity increases the prevalence and incidence of asthma in both children and adults (1–3). Obesity is also common in severe asthma. Indeed, within the The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimes (TENOR) cohort, a U.S. cohort of subjects with severe asthma, 30.7% of the children and 69.3% of the adults were obese versus obesity rates of approximately 20% for children and 35% for adults in the general U.S. population (4). Similarly, in the British Thoracic Society Difficult Asthma Registry, a cohort of adult subjects with severe asthma in the United Kingdom, 48.3% were obese, nearly double the obesity prevalence observed in the general adult U.K. population (25%) (5). The observations that, in obese subjects with asthma, weight loss causes substantial reductions in asthma symptoms, improves asthma control, and reduces airway hyperresponsiveness (6, 7) indicates that, at least for some obese subjects with asthma, obesity is not just a comorbidity, but a causal factor. Data from obese mice also support a causal role for obesity in the development of asthma: obese mice display airway hyperresponsiveness even in the absence of any other inciting stimulus (8–12).

Many obese subjects with asthma have difficulty controlling their asthma (13, 14). Indeed, steroids are less effective in obese than in lean subjects with asthma (15). Conceivably, aspects of the obese state, for example, the systemic inflammation of obesity, reduce steroid efficacy by interfering with corticosteroid signaling pathways (15). However, it is also possible that obese subjects with asthma have a phenotype that is not responsive to steroids: steroids target the immune responses typical of allergic asthma, but many obese subjects with asthma are non-atopic (16, 17). Understanding the mechanistic basis for obese asthma may allow for the development of other therapeutic options that have greater efficacy in this population.

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Obesity-Related Changes in the Gut Microbiome

Estimates are that more than 100 trillion bacteria from over 1,000 different species colonize the human gastrointestinal (GI) tract. The collective genome of these bacteria includes at least 150-fold more genes than are present in the human genome, and has functional capacities that humans lack (18). For example, gut bacteria are capable of metabolizing polysaccharides and dietary starches that are otherwise indigestible. This metabolism results in the production of short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate (19, 20), that can then be used by host cells, especially enterocytes and hepatocytes, for ATP synthesis or conversion to triglycerides or glucose. SCFAs also act as signaling molecules, resulting in effects both inside and outside the GI tract (*see* subsequent discussion). Gut microbiota participate in the synthesis and absorption of some vitamins and minerals, the conversion of primary to secondary bile acids, and the detoxification of some xenobiotics, and contribute to proper intestinal epithelial functioning (21–29).

After birth, there are marked changes in the human gut bacterial community structure that vary depending on Caesarian versus vaginal birth, formula versus breast feeding, host genetics, and especially with the introduction of solid food (30). The community structure begins to stabilize by the age of 2–3 years, but can still be substantially impacted by diet, antibiotic use, changes in geography, age, and environmental exposures (30). Consequently, there are marked interindividual differences in the gut microbiota—differences that are less marked between related individuals, but nevertheless greatly surpass intraindividual differences assessed across time (31).

Impact of Obesity on Gut Microbiota

Obesity alters the distal gut microbiota. In mice, both genetic obesity and high-fat diet (HFD)–induced obesity alter the two most abundant bacterial phyla in the mammalian GI tract, increasing the ratio of Firmicutes to Bacteroidetes (32–36). The composition of the diet itself has a profound effect on gut community structure. In mice fed an HFD, but food restricted to reduce body weight, the gut bacterial community structure is more similar to that in obese HFD-fed mice with unrestricted access to food than to that in mice fed a low-fat diet *ad libitum*, even though the latter have body weights more similar to the HFD-fed food-restricted mice (35). The nature of the dietary fat also matters, as changes in gut microbiota induced by HFD differ depending on whether the fat is derived from lard versus fish oil (37).

The marked interindividual variability in the microbial composition of the human gut makes it more difficult to identify obesity-related effects on gut bacterial community structure in humans than in genetically inbred mice (20). Nevertheless, obesity has been shown to reduce the diversity of gut bacteria in human subjects (31, 38). Studies of diet-induced weight loss also indicate that the Firmicutes-to-Bacteroidetes ratio declines with weight loss in humans (39, 40), consistent with the increased Firmicutes-to-Bacteroidetes ratio observed in obese versus lean mice. Compared with obese subjects matched for initial weight who did not undergo surgery, obese subjects who have undergone Roux-en-Y gastric bypass surgery for weight loss also exhibit reductions in several species of Firmicutes, along with increases in γ proteobacteria (40). Importantly, it may be the functional capacities of gut bacteria, rather than their phylogenetic or taxonomic composition, that is important: compositional differences at the taxonomic level do not necessarily result in differences at the functional level (41). Furthermore, key bacteria can have major health effects, even when those bacteria are present at such low abundance that substantial alterations in their prevalence have minimal impact on overall phylogenetic ratios (42). In this respect, it is important to note that the obese and lean human gut microbiomes do differ with respect to genes involved in carbohydrate, lipid, and amino acid metabolism (31). Similarly, diet-induced weight loss in children with genetic obesity (Prader Willi syndrome) also results in changes in microbial genes related to metabolism (43).

Functional Effects of Obesity-Related Changes in Gut Microbiota

Obesity-related changes in the gut microbiota have important functional consequences for weight gain. Germ-free (GF) mice, mice that are born and raised without exposure to microbes, weigh less than age-, strain-, and sex-matched, conventionally raised (CONV) mice despite greater food consumption and reduced metabolism (44), likely because of reduced microbiota-associated energy harvest from the diet (34, 45). Moreover, GF mice do not gain weight when placed on HFD, but do after bacterial reconstitution by transplant of feces from CONV mice (45, 46). Furthermore, GF mice gain more weight after transplant with fecal contents from CONV obese versus CONV lean mice (34) or after transplant with fecal contents of obese human subjects versus their lean monozygotic twins (47, 48) (Figure 1). Similarly, GF mice colonized with bacteria from feces of obese human subjects who have undergone either dietary or surgically induced weight loss gain less weight than those colonized with bacteria from feces of obese subjects without weight loss intervention (40, 43). In contrast, GF mice transplanted with feces from obese human subjects supplemented with *Christensenellaceae* resulted in reduced weight compared to GF mice transplanted with feces from obese human subjects without *Christensenellaceae* supplementation (49). Finally, probiotics (a source of live micro-organisms that provides health benefits to the host) reduce body mass and body fat in mice with diet-induced obesity (50).

There is less evidence for a role of the gut microbiota in regulation of body weight in human subjects. However, a recent large-scale analysis of glycemic responses to a variety of foods in 800 individuals indicated an association between obesity and the gut community structure (51). In addition, a recent case study noted the development of obesity in a previously lean individual who had undergone a fecal transplantation for the management of *Clostridium difficile*. Notably, the donor was overweight (52). Similarly, Cani and colleagues (53) noted that administration of a prebiotic (a nondigestible food ingredient that stimulates growth of certain gut bacteria, conferring a health benefit to the host) caused increases in several *Bifidobacterium*, *Lactobacillus*, *Roseburia*, and *Faecalibacterium* species, and also caused a significant increase in meal-induced satiety along with increases in the gut-derived hormones (glucagon-like peptide-1 [GLP-1] and peptide YY [PYY]), which are known to cause satiety in humans (53).

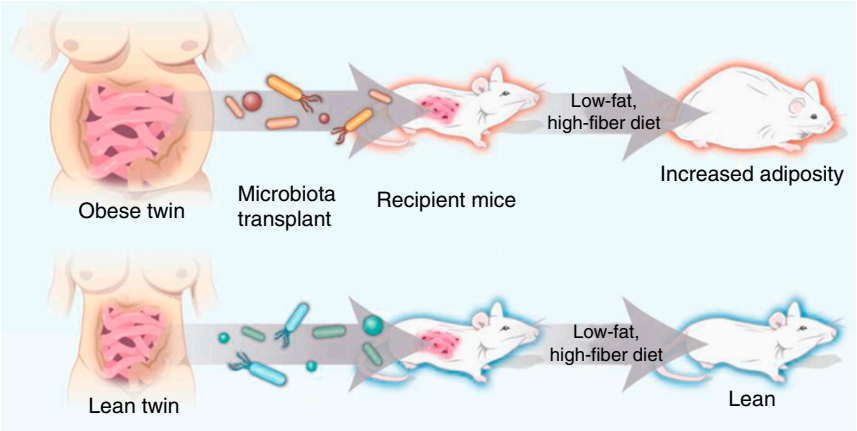

Figure 1. Inoculating germ-free (GF) mice with microbiota from an obese or lean human twin donor results in the GF mice taking on the microbial and adiposity characteristics of the donor. Reproduced from Ref. 48 by permission from the American Association for the Advancement of Science.

Similarly, a report from the Nurses' Health Study indicates that, among the various foods associated with weight loss, yogurt, a probiotic, has the most profound effect (54).

Although differences in energy harvest from the diet account for at least part of the impact of microbiota on body weight (34, 45), the study by Cani and colleagues (53) indicates that microbes can also impact host eating behavior via effects on satiety hormones. However, some satiety hormones can also impact energy harvest. For example, PYY is reduced in GF versus CONV mice (45). PYY inhibits gut motility, and reductions in PYY in GF mice were associated with an increased rate of food transit through the intestines and, hence, less time for energy harvest. Colonization of GF mice also induces central nervous system resistance to leptin (55), another satiety-inducing hormone, whereas prebiotics that reduce the Firmicutes-to-Bacteroidetes ratio increase leptin sensitivity (56). The production of metabolites that activate cannabinoid receptors (which impact eating) is also affected by gut bacteria (57). Finally, taste receptors for fat are altered in the tongues and intestines of GF versus CONV mice (58), indicating that microbes also impact food preferences.

Microbiome-dependent changes in metabolism may also contribute to the role of the microbiome in obesity. Gut microbiota regulate the intestinal epithelial expression of Fiaf, an angiopoietin-like protein. Fiaf alters lipoprotein lipase activity (44) in adipose tissue, and also impacts expression of genes that regulate mitochondrial oxidation of fatty acids (59).

Obesity-related changes in gut bacteria also impact other aspects of the obese phenotype. For example, antibiotics reverse the insulin resistance caused by high-fat feeding (60), suggesting that obesity-related changes in the microbiome may contribute to type 2 diabetes. Indeed, a small study performed in human subjects indicates that transfer of gut microbiota from nondiabetic into diabetic individuals results in improved insulin sensitivity (61). Furthermore, individual glycemic responses to a large variety of foods can be predicted by components of the gut microbiome assessed in fecal samples (51). Consistent with these observations, probiotic treatments also impact the insulin resistance associated with obesity in mice (62).

Chronic, low-grade systemic inflammation is another consequence of obesity. The adipose tissue of obese mice and obese human subjects is infiltrated with activated macrophages producing a variety of proinflammatory cytokines and chemokines that enter the systemic circulation. Increasing evidence points to a role for the microbiota in these events. For example, HFD feeding results in an increase in the proportion of bacteria containing LPS (endotoxin) in the gut and alters the permeability of the intestinal epithelium, resulting in systemic endotoxemia that contributes to the adipose tissue inflammation. Thus, proinflammatory cytokine levels are elevated by HFD in wild-type, but not Toll-like receptor 4–deficient or myeloid differentiation primary response gene 88 (MyD88)-deficient, mice that lack effective LPS signaling capacities (37, 63, 64). In addition, treatment with *Akkermansia muciniphila*, bacteria that are typically attenuated in the obese, reverses both endotoxemia and adipose tissue inflammation, in HFD-fed mice (65). Other probiotic treatments also affect the systemic inflammation associated with obesity in mice (66). Given that the systemic inflammation of obesity may also contribute to obesity-associated asthma (67), such results suggest the potential efficacy of probiotic therapeutics in obese subjects with asthma.

Mechanistic Basis for Functional Consequences of Obesity-Related Changes in Gut Microbiota: the Metabolome

As described previously here, endotoxemia may mediate some of the effects of obesity on outcomes such as systemic inflammation and insulin resistance. Given the potential for endotoxin to impact asthma-related outcomes (68), obese microbiome–related changes in endotoxin might also impact asthma. The microbiome also has broad effects on the immune system, including the generation of regulatory T cells (Tregs) and the development of IL-17A–expressing cells (69). As recently reviewed, such effects could also impact obesity-related asthma (70). However, in obesity, there are also profound changes in the metabolome, the set of small-molecule metabolites present in a given biological fluid, cell type, or tissue. Importantly, accumulating evidence suggests a key role for the microbiome in such metabolic changes. Whether and how such changes might contribute to obese asthma remains to be established.

The Metabolome Is Altered in Obesity

Both in humans and in rodents, the metabolomes of the liver, serum, urine, and adipose tissue are altered by obesity (71–80). Given that insulin resistance is common in obesity, it is perhaps not surprising that glucose, lactate, glycerol, fatty acids, and β-hydroxybutyrate are increased in the blood of obese versus lean subjects. Blood metabolomics also consistently indicate

obesity-related alterations in branched-chain amino acid metabolites (80–82). Because receptors for many fatty acids (G protein–coupled receptor [GPR] 40, GPR41, GPR49, GPR84, and GPR120), for lactate (hydroxycarboxylic acid [HCA1]/GPR81), and for β-hydroxybutyrate (HCA2/GPR109A) exist (83, 84), and because such small metabolites have the capacity to diffuse across pulmonary capillaries, obesity-related changes in these moieties could impact lung function directly via activation of these receptors.

Gut Microbiota Impact the Metabolome

Gut microbiota metabolize dietary foodstuffs to produce a huge variety of small metabolites that can diffuse across the gut into the circulation, where some are further metabolized by host enzymes, resulting in bacterial–mammalian cometabolites. Thus, gut bacterial–derived metabolites can affect not only the GI tract, but also other target organs, leading to the description of the gut microbiota as an endocrine organ (85). For example, trimethylamine, a microbial-dependent metabolite derived from dietary choline, is oxidized in the liver to produce trimethylamine *N*-oxide (TMAO). Serum concentrations of TMAO are linked to atherosclerosis and cardiovascular disease risk (86, 87). Similarly, when the cecal contents of atherosclerosis-prone mice are transplanted into antibiotic-treated mice, the mice develop enhanced choline diet–induced atherosclerosis and TMAO (88). Even the brain is impacted by bacterial metabolites. Serum concentrations of the bacterial-dependent metabolite, 4-ethylphenylsulfate, are markedly elevated in mouse models of autism. Importantly, treatment with *Bacteroides fragilis* in the food reverses these elevations in 4-ethylphenylsulfate and also improves autism-like behavior (89).

Microbiota affect the metabolomes of the intestines, urine, liver, brain, and kidney (27, 90–97). The blood metabolome is also affected. For example, studies using GF mice and studies using antibiotic treatment indicate effects of gut microbiota on serum levels of many bacterial-derived metabolites, including SCFA, pipecolate, choline, phenol sulfate, and hippurate (90, 98, 99). Thus, the altered gut microbiome of obesity may affect metabolites that circulate to the lungs and affect airway function. Subsequently here, we discuss the role of the microbiota in the generation of two groups of metabolites: SCFAs and bile acids, as well as the potential for these metabolites to impact obese asthma.

SCFAs. As discussed previously here, gut bacteria are capable of fermenting polysaccharides and dietary starches that are otherwise indigestible, leading to the production of the SCFAs: butyrate, propionate, and acetate (19, 20). In the GI tract, SCFAs are produced from dietary polysaccharides via bacterial metabolism. Indeed, compared with CONV mice, GF mice have reduced intestinal SCFAs and excrete significantly more calories in their feces in the form of indigestible polysaccharides (20). Consistent with these observations, colonizing GF mice with *Bacteroides thetaiotaomicron* increases production of SCFAs in GF rodents (100). Similarly, mice fed a high-fiber diet have increased gut *Bifidobacterium*, a bacterium that ferments dietary fiber to form SCFAs, and increased circulating SCFAs (99). Most SCFA production occurs in the distal colon and cecum, and both the makeup of the microbiota present and the transit time through the colon impact the amount of SCFAs produced (101).

Increasing data support a relationship between the microbiome, SCFAs, and obesity. SCFAs are higher in the cecal contents of genetically obese mice. Increased fecal SCFAs are also observed in human obesity (101). In twins discordant for obesity, the microbiome of the obese twin is enriched for genes involved in carbohydrate fermentation to SCFAs (31). Given the ability of SCFAs to provide an energy source to the host, one might expect that elevated SCFA production in obesity would contribute to weight gain. Nevertheless, exogenously administered SCFAs actually reduce weight gain in mice (102). The ability of SCFAs to increase the production of satiety hormones, including GLP-1, PYY, and leptin (103, 104), and to increase energy expenditure (105), likely explains this apparent conundrum.

SCFAs have multiple effects that could impact obese asthma (Figure 2). First, SCFAs play a role in the regulation of T cells, both in the GI tract and in peripheral tissues. For example, exogenous administration of SCFA promotes the development of Tregs (106). Reductions of Tregs in adipose tissue are thought to contribute to the systemic inflammation of obesity (107). Second, SCFAs stimulate intestinal epithelial proliferation and differentiation (108), and could also contribute to repair of the epithelial cell damage that is typical of asthma. SCFA-mediated changes in epithelial barrier function could also impact the systemic endotoxemia of obesity. Antiinflammatory effects of SCFAs could also counter the effects of this endotoxemia, as SCFAs inhibit LPS-induced NF-κB activation and increases in TNF-α in neutrophils and macrophages (101, 109). Effects of SCFAs are mediated both by binding of SCFAs to GPRs, including GPR41, GPR43, and GPR109A, which vary in their sensitivity to acetate, propionate, and butyrate, and by inhibition of histone deacetylase (101, 110–112).

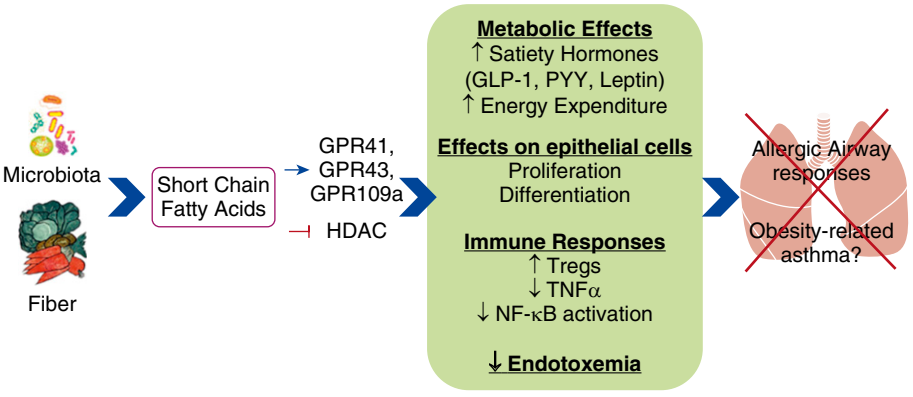

Figure 2. Schematic representation of ways in which short-chain fatty acids from microbiota metabolism of dietary fiber may prevent allergic airway responses and obesity-related asthma. GLP-1, glucagon-like peptide-1; HDAC, histone deacetylase; PYY, peptide YY; Tregs, regulatory T cells.

Although there are, as yet, no studies of the role of SCFAs in obesity-related asthma, data do suggest a role for the gut microbiome, and for SCFAs in particular, in modulating allergic asthma. GF mice, which have a reduced ability to produce SCFAs (20), develop greater allergic airways responses than CONV mice (113, 114). Furthermore, both elevations in circulating SCFAs induced by high-fiber feeding and exogenously administered propionate protect against allergic airways inflammation in mice, and this protective effect is lost in GPR41-deficient mice (99). Similarly, low fiber–fed mice with circulating levels of SCFAs have increased allergic airways responses (99). These effects of SCFAs appear to occur at the level of the bone marrow and dendritic cell precursors that impact the immune response to allergen.

Bile acids. Primary bile acids, such as cholate and chenodeoxycholate, are synthesized from cholesterol and conjugated with either glycine (humans) or taurine (mice) in the liver. Bile is then secreted via the bile duct into the duodenum in response to hormonal signals initiated by eating. In the intestines, bile acids contribute to the digestion of dietary fat by acting as emulsifiers. In the lower GI tract, most of the bile acids are absorbed back into the circulation and returned to the liver, where they are taken up and re-excreted (the enterohepatic circulation), although some escape reuptake and circulate in the systemic blood. The enterohepatic circulation thus prevents loss of cholesterol-containing moieties in the feces (40, 115, 116).

Gut microbes both modify and are modified by bile acids (40, 115, 116). Gut bacteria deconjugate and dehydroxylate bile acids, resulting in the formation of secondary bile acids. Consequently, there is an increase in the ratio of conjugated to unconjugated bile acids in GF and antibiotic-treated mice (117). Bile acids themselves have bactericidal properties via their detergent properties on bacterial membranes, although certain bacteria (e.g., *Bilofilia wadsorthia*) actually thrive in environments rich in bile acids (118). Thus, changes in the release of bile acids, for example, in response to HFDs, can alter the community structure of the gut microbiome. Indeed there are substantial changes in the gut microbiome in rats fed a diet containing high levels of cholate (119).

In addition to their bacteriostatic and emulsifying actions, bile acids also have a signaling role. Bile acid binding to two receptors, farnesoid X receptor (FXR), a nuclear receptor, and to a GRP, Takeda G protein-coupled receptor 5 (TGR5), mediate these effects. FXR- and TGR5-mediated signaling events contribute to beneficial effects of bile acids against obesity and obesity-related conditions (Figure 3). For example, bile acids increase energy expenditure through TGR5-mediated changes in thyroid hormone synthesis (120). Bile acids also cause TGR5-dependent secretion of the satiety hormone, PYY (121). In the liver, bile acid–induced activation of FXR results in reduced fatty acid synthesis and decreases circulating triglycerides (120). FXR activation also inhibits hepatic gluconeogenesis. Indeed, FXR-deficient mice are insulin resistant (122). A major role for a bile/microbiome axis in obesity was also revealed by a study showing that GF mice receiving the fecal microbiota from an obese twin displayed not only a greater fat mass than mice receiving gut microbes from the lean twin, but also reduced levels of several bile acids and reduced FXR-dependent gene transcription in the ileum and the liver (47).

Bariatric surgery results in increased circulating bile acids (115) and, in mice with HFD-induced obesity, these bile acids appear to mediate reduced eating, subsequent weight loss, and improved glucose tolerance, because these effects are reduced in FXR-deficient mice (123). Bariatric surgery alters gut microbial communities, and there are also differential effects of bariatric surgery on the gut microbiome in FXR versus wild-type mice (123). Bariatric surgery also improves obesity-associated asthma (6), but whether or not bile acid– and/or microbiome-mediated changes are involved in these events remains to be determined. However, it is interesting to note that a recent metabolomic profiling of plasma from subjects with asthma versus healthy subjects identified bile acids (taurocholate and

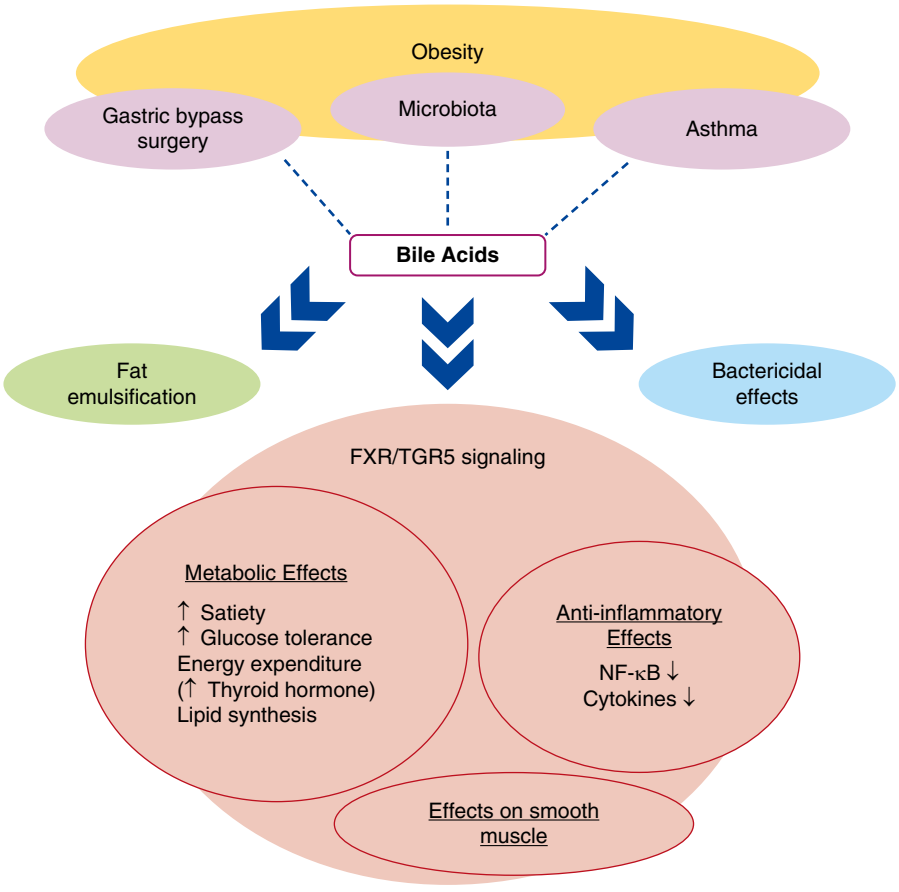

Figure 3. Schematic representation of ways in which bile acid modifications in obesity may impact obesity-related asthma. FXR, farnesoid X receptor; TGR5, Takeda G protein–coupled receptor 5.

glycodeoxycholate) among the metabolites that were affected by asthma (124).

Bile acids also have antiinflammatory effects that may be relevant for asthma (125). For example, in macrophages, TGR5 activation causes elevations in cyclic adenosine monophosphate (cAMP) that inhibits NF-κB–mediated induction of proinflammatory cytokines by LPS (126). The observation that TGR5 agonists attenuate atherosclerosis in TGR5-sufficient, but not TGR5-deficient, mice (127) indicates that there are important functional consequences of such antiinflammatory effects of bile acids.

Finally, bile acids, via TGR5 signaling, promote relaxation of gastric smooth muscle (128). TGR5-dependent activation of Gαs and consequent increases in cAMP mediate this relaxation. Because airway smooth muscle also relaxes in response to elevations in cAMP, it is conceivable that changes in bile acids could also impact the bronchoconstriction of asthma.

Conclusions

Obesity alters the gut bacterial community structure. Such changes could play a role in obesity-related asthma via alterations in production of bacterial-derived or modified metabolites, such as SCFAs or bile acids. A role for the microbiome in obesity-related asthma has both public health and therapeutic implications. The gut microbiome is shaped by early life events, including mode of delivery, breastfeeding, diet, and antibiotic use. Understanding the impact of these factors on the development of both obesity and asthma could alter early life decisions that impact long-term disease development. Greater understanding of the role of microbiota in obesity-related asthma could also pave the way for the development of novel microbiota-based treatments for this difficult-to-treat group. For example, it is conceivable that altering the gut microbiota with probiotics, prebiotics, or even fecal transplants could ameliorate obesity-related asthma or improve the ability of obese subjects with asthma to respond to standard asthma therapeutics. Indeed, such interventions are effective against other obesity-related conditions (61, 129–131). Microbiota-based therapies that impact weight might also prove effective, given the efficacy of weight loss in obese subjects with asthma (6). To the extent that obesity-related changes in SCFAs or bile acids are important, interventions that promote the survival of SCFA-producing bacteria, high-fiber diets, or even direct administration of SCFAs, or GRP41/43, TGR5, or FXR ligands might also prove effective. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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