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LETTER TO THE EDITOR

Gut microbiota-derived metabolites are novel targets for improving insulin resistance

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Abstract

The gut microbiota plays a key role in metabolic diseases. Gut-microbiota-derived metabolites are found in different dietary sources, including: Carbohydrate (acetate, propionate, butyrate, also known as short-chain fatty acids, as well as succinate); protein (hydrogen sulfide, indole, and phenylacetic acid); and lipids (resveratrol-, ferulic acid-, linoleic acid-, catechin- and berry-derived metabolites). Insulin resistance, which is a global pandemic metabolic disease that progresses to type 2 diabetes mellitus, can be directly targeted by these metabolites. Gut-microbiota-derived metabolites have broad effects locally and in distinct organs, in particular skeletal muscle, adipose tissue, and liver. These metabolites can modulate glucose metabolism, including the increase in glucose uptake and lipid oxidation in skeletal muscle, and decrease in lipogenesis and gluconeogenesis associated with lipid oxidation in the liver through activation of phosphatidylinositol 3-kinase - serine/threonine-protein kinase B and AMP-activated protein kinase. In adipose tissue, gut-microbiota-derived metabolites stimulate adipogenesis and thermogenesis, inhibit lipolysis, and attenuate inflammation. Importantly, an increase in energy expenditure and fat oxidation occurs in the whole body. Therefore, the therapeutic potential of current pharmacological and non-pharmacological approaches used to treat diabetes mellitus can be tested to target specific metabolites derived from intestinal bacteria, which may ultimately ameliorate the hyperglycemic burden.

Key Words: Insulin resistance; Gut microbiota; Metabolites; Host metabolism; Metabolic organs; Novel targets

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Core Tip: The gut-microbiota-derived metabolites play a key role in metabolic diseases. Insulin signaling pathways are directly targeted by these metabolites, as they promote an increase in glucose uptake and lipid oxidation in skeletal muscle; a decrease in lipogenesis and gluconeogenesis associated with an increase in lipid oxidation in the liver; and an improvement in thermogenesis and inflammation in the adipose tissue. Collectively, these findings pave the way for the development of novel drugs or for investigation of the therapeutic potential of drugs currently used to treat insulin resistance, targeting the gut-microbiota-derived metabolites.

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TO THE EDITOR

We read with interest the recent publication by Jang and Lee[1] on the relationship of mechanisms linking the gut microbiota-derived metabolites to insulin resistance published in this journal.

The gut microbiota plays a key role in metabolic diseases. Gut-microbiota-derived metabolites are found in different dietary sources, including: Carbohydrate (acetate, propionate, butyrate, and succinate); protein (hydrogen sulfide, indole, and phenylacetic acid); and lipids (resveratrol-, ferulic acid-, linoleic acid-, cathecin- and berry-derived metabolites). Insulin signaling pathways are directly targeted by these metabolites. Therefore, gut-microbiota-derived metabolites, in particular, the short-chain fatty acids (SCFAs), increase glucose uptake and lipid oxidation in skeletal muscle, whereas in the liver, SCFAs decrease lipogenesis and gluconeogenesis, increasing the lipid oxidation through activation of phosphatidylinositol 3-kinase - serine/threonine-protein kinase B (PI3K-AKT-PKB) and AMP-activated protein kinase. In adipose tissue, SCFAs stimulate adipogenesis and thermogenesis, inhibit lipolysis, and attenuate inflammation. Therefore, an increase in energy expenditure and fat oxidation occurs in the whole body. Collectively, these findings pave the way for the development of novel drugs or for investigation of the therapeutic potential of drugs currently used to treat insulin resistance, targeting the gut-microbiota-derived metabolites.

Notably, preclinical models and clinical studies substantiate the interaction between intestinal microbiota and the pathophysiology of insulin resistance in type 2 diabetes mellitus (DM)[2-4].

Therefore, this current article provides an overview of the important role of the specific microbiota-derived compounds in insulin-responsive tissues, acting as risk factors or protectors for the development of insulin resistance, and highlights the biologic implications of the muscle–liver–adipose tissue axis interaction.

Even though the authors documented the potential role of some bacterial metabolites as regulators of metabolic functions in the body, such as SCFAs derived from carbohydrates (propionate, butyrate and acetate), and the protein- and lipid-derived metabolites, in modulating pathways of insulin signaling, the impact of these bacterial metabolites on host metabolism warrants further investigation.

Importantly, succinate is a metabolite of the tricarboxylic acid cycle and is produced equally by microbiota and the host[5]. Although this metabolite contributes to improving glucose homeostasis through the activation of intestinal gluconeogenesis [6], in obese individuals, high levels of this circulating metabolite are documented[5]. Furthermore, the imbalance of higher relative abundance of succinate-producing bacteria (Prevotellaceae and Veillonellaceae) and lower relative abundance of succinate-consuming bacteria Odoribacteraceae and Clostridaceae) may promote an increase in succinate levels and, ultimately, impaired glucose metabolism. These authors also pointed out succinate as having a potential role in metabolic-associated cardiovascular disorders and obesity. Additionally, succinate acts as an immunogenic molecule, identified as damage-associated molecular patterns. This molecule is recognized by immune cells and stabilizes hypoxia-inducible factor-1α through its G-protein coupled receptor (succinate receptor 1/SUCNR1 or GPR19), which leads to the

proinflammatory differentiation of T lymphocytes, and production of cytokines through interaction with Toll-like receptor ligands in dendritic cells[7,8]. Collectively, these findings may promote an enhancement of insulin resistance and DM burden.

Furthermore, hydrogen sulfide (H_2S) and the role of sulfur-reducing bacteria from the intestinal microbiota have gained insights into the physiological implications of host glycemic control[9]. Thus, H_2S metabolite may protect against oxidative stress by restoring reduced glutathione (GSH) and scavenging of mitochondrial reactive oxygen species, inducing pro-survival/angiogenesis signaling pathway (STAT3, signal transducer and activator of transcription 3), and promoting immunomodulation (inhibition/activation of nuclear factor-κB) and vasodilation (activation of K_{ATP} ion channel)[10]. However, the balance between therapeutic and harmful effects of H_2S should be considered when targeting that metabolite, as H_2S either endogenous or exogenous, as well as that produced by the gut microbiota, promotes or inhibits a variety of characteristics in mucosal microbiota biofilms[11]. Depending on H_2S concentration, in particular, when the gut microbiota produces an excessive amount, it may cause mucus disruption and inflammation in the colon and contribute to cancer. Conversely, low levels of H_2S directly stabilize mucus layers, prevent fragmentation and adherence of the microbiota biofilm to the epithelium, inhibit the release of invasive opportunistic pathogens or pathobionts, and prevent inflammation and tissue injury[11]. Moreover, H_2S overproduction is a causative factor in the pathogenesis of β-cell death in DM due to increased levels of reactive oxygen and nitrogen species, whereas its deficiency, as a result of increased H_2S consumption by hyperglycemic cells, may lead to endothelial dysfunction, and kidney and heart diseases[12].

As we learn more about gut-microbiota-derived metabolites, we will better understand how to target these metabolites. Thus, acetate, which is involved in host energy, substrate metabolism, and appetite *via* secretion of the gut hormones [glucagon-like peptide (GLP) and peptide YY], may be increased by oral acetate administration (vinegar intake), colonic acetate infusions, acetogenic fibers and acetogenic probiotic administration[13]. These strategies may both decrease whole-body lipolysis and systemic proinflammatory cytokine levels, and increase energy expenditure, insulin sensitivity, and fat oxidation, which contributes to weight control and glucose homeostasis. Probiotics (live microorganisms) act as microbiome modulators and confer a health benefit, as demonstrated by the capacity of selected probiotic strains (lactobacilli and enterococci) to increase SCFA production; in particular, propionate and butyrate[14]. As reviewed elsewhere, probiotic administration (*Bifidobacterium pseudocatenulatum*, *Lactobacillus plantarum*, or the formula VSL#3) in preclinical models of obesity led to an increase in the intestinal barrier function, a reduction in the endotoxemia, acceleration in metabolism, and suppression of body weight gain and insulin resistance *via* modulation of the gut microbiota composition and SCFA production[15]. Probiotics may also ameliorate glucose homeostasis and lipid profile in diabetic mice[15].

From a clinical point of view, obese children treated with the probiotic *Lactobacillus casei* shirota for 6 mo presented with loss of weight, improved lipid metabolism, and an increase in the number of *Bifidobacterium* spp. and acetate concentration in the feces [16]. Likewise, patients with type 2 DM treated with probiotics containing *Lactobacillus acidophilus* La-5 and *Bifidobacterium animalis* subsp. lactis BB-12 for 6 wk had improved glucose and lipid profiles, which were associated with lower levels of systemic inflammation and increased concentration of acetate[17]. Additionally, modification of gut microbiota by dietary weight loss intervention decreased circulating succinate levels and improved the metabolic profile in a cohort of individuals with type 2 DM and obesity[6].

Pharmacological interventions or xenobiotics may also have effects on gut microbiota. Metformin is the most frequently administered medication to treat patients with insulin resistance and type 2 DM. This drug may alter the gut microbiota composition through an increase in the Bacteroidetes and Verrucomicrobia phyla and the mucin-degrading *Akkermansia muciniphila*, *Bacteroides*, and *Escherichia* genera, as well as in butyrate and propionate production, emphasizing maintenance of the integrity of the intestinal barrier, regulation of bile acid metabolism and improvement in glucose homeostasis[18,19]. Importantly, metformin may have these benefits in newly diagnosed DM[20].

Sodium-glucose cotransporter 2 inhibitors represent the most recently approved class of oral medications for the treatment of type 2 DM. Dapagliflozin decreased the Firmicutes-to-Bacteriodetes ratio in diabetic mice, which was correlated with improvement in vascular function[21]. In a rodent model of type 1 DM, inhibition of SGLT2 reduced the intermediate metabolite succinate and increased butyrate levels, as well as decreased norepinephrine content in the kidney[22]. Hence, the impact of

SGLT2 inhibitors on the gut microbiota is an area of active research.

Likewise, GLP-1 agonists reduced the abundance of the species of the Firmicutes phylum (Lachnospiraceae and Clostridiales) and increased the abundance of the species representing the Proteobacteria (*Burkholderiales bacterium* YL45) and Verrucomicrobia (*Akkermansia muciniphila*), as well as Firmicutes (Clostridiales and Oscillospiraceae) phyla in obese mice[23]. In particular, body weight loss was associated with increased abundance of *Akkermansia muciniphila*, a mucin-degrading SCFA-producing species, whose abundance is decreased in obesity and has a negative correlation with markers of gut permeability and inflammation. Notably, the GLP-1 agonist liraglutide can prevent weight gain by modulating gut microbiota composition in both obese and diabetic obese animals[24].

In the cardiometabolic disease setting, lipid-lowering drugs, such as statins, may also play an important role in modulating gut microbiota. *In vitro* studies have documented increased levels of SCFA production, including propionate, butyrate and acetate[25]. These drugs may increase the abundance of the *Bacteroides*, *Butyricimonas* and *Mucispirillum* genera, which is associated with a decrease in the inflammatory response, including lower levels of interleukin (IL)-1β and IL-6, and higher levels of transforming growth factor β-1 in the ileum, and improved hyperglycemia[26]. In humans, obesity is associated with a microbiota signature based on the abundance of the *Bacteroides* genus profile, displaying the lowest abundances of *Akkermansia* and *Faecalibacterium*, as well as a decrease in the butyrate production potential[27]. Importantly, statin therapy resulted in a lower prevalence of a proinflammatory microbial community type in obese individuals.

In conclusion, the gut microbiota imbalances and maladaptive responses have been implicated in the pathology of insulin resistance, DM, and obesity[28]. Host-gut microbiota interaction is suggested to play a contributory role in the therapeutic effects of antidiabetics, statins, and weight-loss-promoting drugs. Therefore, additional studies combining untargeted metabolomics and proteomics are essential to identify further microbial metabolites or proteins and to determine how they interact with the host targets in improving host metabolism.

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