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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Mechanisms linking gut microbial metabolites to insulin resistance

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Abstract

Insulin resistance is the rate-limiting step in the development of metabolic diseases, including type 2 diabetes. The gut microbiota has been implicated in host energy metabolism and metabolic diseases and is recognized as a quantitatively important organelle in host metabolism, as the human gut harbors 10 trillion bacterial cells. Gut microbiota break down various nutrients and produce metabolites that play fundamental roles in host metabolism and aid in the identification of possible therapeutic targets for metabolic diseases. Therefore, understanding the various effects of bacterial metabolites in the development of insulin resistance is critical. Here, we review the mechanisms linking gut microbial metabolites to insulin resistance in various insulin-responsive tissues.

Key Words: Insulin resistance; Skeletal muscle; Liver; Adipose tissue; Intestine; Gut bacterial metabolites

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Core Tip: Since the gut microbiota has been implicated in host energy metabolism and metabolic diseases, understanding mechanisms linked to insulin resistance is a first step in discovery of new drugs and novel targets against metabolic diseases. Here, we review the mechanisms linking gut microbial metabolites to insulin resistance in major target tissues of insulin.

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INTRODUCTION

Insulin resistance is a pathological state in which tissues do not respond normally to insulin in the process of glucose metabolism. Insulin is an endocrine hormone that binds to insulin receptors on the plasma membrane of target cells, which induces an anabolic response to nutrient availability[1]. Insulin directly regulates glucose homeostasis by acting on skeletal muscle, the liver, and adipose tissue. These tissues have different functions in metabolic homeostasis that are regulated *via* tissue-specific insulin signaling pathways. In skeletal muscle, insulin stimulates glucose uptake and storage by increasing the expression of glucose transporters (GLUTs) and glycogen synthesis[1,2]. In the liver, insulin activates glycogen synthesis and *de novo* lipogenesis and suppresses gluconeogenesis[1,2]. In adipose tissue, insulin suppresses lipolysis and increases both glucose and fatty acid uptake and lipogenesis[1,2]. In the insulin-resistant state, peripheral glucose disposal is impaired and hepatic gluconeogenesis and adipose lipolysis are not suppressed by insulin. Insulin resistance increases circulating glucose level, which results in increased insulin production in β cells as a compensatory response and hyperinsulinemia, leading to a vicious cycle that promotes further insulin resistance[1,3]. Non-treated and prolonged insulin resistance causes hyperglycemia and type 2 diabetes, and can lead to its complications including hyperlipidemia, metabolic syndrome, nonalcoholic fatty liver disease, and cardiovascular diseases[3,4].

Various factors have been implicated in the pathogenesis of insulin resistance, including genetic predisposition, aging, obesity, and a sedentary lifestyle. More recently, the gut microbiota has been considered to be a key factor leading to the insulin resistance[5]. The gut microbiota regulates host dietary intake, energy metabolism, and energy expenditure[6]. Changes in the composition of the intestinal bacteria might alter energy metabolism and exert various effects on the important metabolic organs, such as skeletal muscle, the liver, and adipose tissue[6]. In addition, the gut microbiota produces thousands of metabolites that accumulate in the gastrointestinal system and can be transferred to distant organs[7]. Lots of recent metabolomics studies examined the association of gut microbiota-derived metabolites with metabolic disease and their effects on host metabolism[8-10]. Therefore, understanding the various effects of bacterial metabolites in the development of insulin resistance becomes critical for discovering novel targets and developing new drugs against metabolic diseases. In this review, we review studies that provide evidence for a relationship between gut bacterial metabolites and insulin resistance, and summarize current mechanisms linking gut microbial metabolites to the development of insulin resistance in various metabolic organs, including skeletal muscle, liver, adipose tissue, and intestine.

EFFECTS OF GUT BACTERIAL METABOLITES ON THE PATHOGENESIS OF INSULIN RESISTANCE

We split this section into four parts for each metabolic organ, and briefly describe the pathophysiology of insulin resistance first followed by further discussions on current mechanisms linking gut microbial metabolites to the development of insulin resistance. The mechanisms for each organ are graphically presented in Figure 1 and the studies for each metabolite are summarized in Table 1.

Skeletal muscle

Skeletal muscle is the primary organ for glucose disposal, accounting for up to 70% of glucose uptake in our body[11]. Insulin promotes glucose uptake in skeletal muscle by translocating the GLUT4 to the plasma membrane[12]. In insulin-sensitive skeletal muscle, the insulin receptor substrate 1-phosphoinositide-3-kinase (PI3K)-AKT arm of the insulin signaling cascade is activated, which increases glucose uptake and glycogen synthesis[1]. In insulin-resistant skeletal muscle, proximal insulin signaling

Table 1 The effects of diet-derived gut bacterial metabolites on the pathogenesis of insulin resistance in various organs

Category	Metabolite	Target organ	Effects	Ref.	
Carbohydrate					
Fiber-derived	Acetate	Skeletal muscle	Increased lipid oxidation <i>in vivo</i>	Yamashita <i>et al</i> [75]	
		Liver	Decreased lipogenesis <i>in vivo</i>	den Besten <i>et al</i> [47] and Yamashita <i>et al</i> [51]	
			Increased lipid oxidation <i>in vivo</i>	den Besten <i>et al</i> [47], Yamashita <i>et al</i> [51], Kondo <i>et al</i> [52] and Sahuri-Arisoylu <i>et al</i> [53]	
		Adipose tissue	Stimulated adipogenesis <i>in vitro</i>	Ge <i>et al</i> [60]	
			Inhibited lipolysis <i>in vitro</i> and <i>in vivo</i>	Hong <i>et al</i> [59], Ge <i>et al</i> [60] and Jocken <i>et al</i> [61]	
			Increased browning <i>in vitro</i> and <i>in vivo</i>	Sahuri-Arisoylu <i>et al</i> [53] and Hanatani <i>et al</i> [73]	
		Whole body	Increased energy expenditure and fat oxidation <i>in vivo</i> and in humans	den Besten <i>et al</i> [47], Canfora <i>et al</i> [77] and van der Beek <i>et al</i> [78]	
		Propionate	Liver	Suppressed gluconeogenesis <i>in vitro</i>	Yoshida <i>et al</i> [29]
				Decreased lipogenesis <i>in vivo</i>	den Besten <i>et al</i> [47]
				Increased lipid oxidation <i>in vivo</i>	den Besten <i>et al</i> [47]
	Adipose tissue		Increased adipogenesis <i>in vitro</i>	Ge <i>et al</i> [60]	
			inhibit lipolysis <i>in vitro</i> and <i>in vivo</i>	Hong <i>et al</i> [59] and Ge <i>et al</i> [60]	
			Improved inflammation in <i>ex vivo</i>	Al-Lahham <i>et al</i> [66]	
	Intestine		Promoted gluconeogenesis <i>in vivo</i>	De Vadder <i>et al</i> [91]	
	Whole body		Increased energy expenditure and fat oxidation <i>in vivo</i> and in humans	den Besten <i>et al</i> [47], Canfora <i>et al</i> [77] and Chambers <i>et al</i> [79]	
	Butyrate		Skeletal muscle	Increased lipid oxidation <i>in vitro</i> and <i>in vivo</i>	Gao <i>et al</i> [48]
			Liver	Decreased lipogenesis <i>in vivo</i>	den Besten <i>et al</i> [47]
		Increased lipid oxidation <i>in vivo</i>		den Besten <i>et al</i> [47], Gao <i>et al</i> [48] and Mollica <i>et al</i> [49]	
		Adipose tissue	decreased lipolysis <i>in vitro</i>	Ohira <i>et al</i> [67]	
			Improved inflammation <i>in vitro</i>	Ohira <i>et al</i> [67]	
			Increased thermogenesis <i>in vivo</i>	Gao <i>et al</i> [48] and Li <i>et al</i> [74]	
		Intestine	Promoted gluconeogenesis <i>in vitro</i> and <i>in vivo</i>	De Vadder <i>et al</i> [91]	
		Whole body	Increased energy expenditure and fat oxidation <i>in vivo</i> and in humans	den Besten <i>et al</i> [47], Gao <i>et al</i> [48] and Canfora <i>et al</i> [77]	
		Succinate	Intestine	Promoted gluconeogenesis <i>in vivo</i>	De Vadder <i>et al</i> [92]
Protein					
Protein-derived	Hydrogen sulfide	Liver	Increased gluconeogenesis <i>in vitro</i>	Zhang <i>et al</i> [32]	
			Decreased glycogen synthesis <i>in vitro</i>	Zhang <i>et al</i> [32]	
	Indole	Adipose	Increased inflammation <i>in vivo</i>	Virtue <i>et al</i> [10]	

		tissue		
	Indole-3-carboxylic acid	Adipose tissue	Increased inflammation <i>in vivo</i>	Virtue <i>et al</i> [10]
	Phenylacetic acid	Liver	Increased lipogenesis <i>in ex vivo</i> and <i>in vivo</i>	Hoyles <i>et al</i> [46]
Lipid and others				
Linoleic acid-derived	10-oxo-12(Z)-octadecenoic acid	Adipose tissue	Induced adipogenesis <i>in vitro</i>	Goto <i>et al</i> [55]
			Increased thermogenesis <i>in vivo</i>	Kim <i>et al</i> [81]
	Conjugated linoleic acid	Adipose tissue	Increased energy expenditure	Takahashi <i>et al</i> [82], Park <i>et al</i> [83] and Lee <i>et al</i> [84]
Ferulic acid-derived	Ferulic acid 4-O-sulfate and Dihydroferulic acid 4-O-sulfate	Skeletal muscle	Increased glucose uptake <i>in vitro</i>	Houghton <i>et al</i> [19]
Resveratrol-derived	<i>Trans</i> -resveratrol 4'-O-glucuronide and <i>Trans</i> -resveratrol 3-O-sulfate	Skeletal muscle	Increased glucose uptake <i>in vitro</i>	Houghton <i>et al</i> [19]
Berries-derived	Isovanillic acid 3-O-sulfate	Skeletal muscle	Increased glucose uptake <i>in vitro</i>	Houghton <i>et al</i> [19]
Catechin-derived	4-hydroxy-5-(3,4,5-trihydroxyphenyl) valeric acid, 5-(3,4,5-trihydroxyphenyl)- γ -valerolactone, and 5-(3-hydroxyphenyl) valeric acid	Skeletal muscle	Increased glucose uptake <i>in vitro</i>	Takagaki <i>et al</i> [22]
Catechin-derived	5-(3,5-dihydroxyphenyl)- γ -valerolactone	Skeletal muscle	Increased glucose uptake <i>in vitro</i> and <i>in vivo</i>	Takagaki <i>et al</i> [22]
Bacteria-derived	Extracellular vesicles	Skeletal muscle	Decreased glucose uptake <i>in vivo</i>	Choi <i>et al</i> [20]
Choline-derived	Trimethylamine N-oxide	Liver	Increased gluconeogenesis <i>in ex vivo</i> and <i>in vivo</i>	Chen <i>et al</i> [33] and Gao <i>et al</i> [43]
		Adipose tissue	Promoted inflammation <i>in vivo</i>	Gao <i>et al</i> [43]

events are impaired, which blocks the function of insulin to translocate GLUT4 to plasma membrane and to stimulate glycogen synthesis[1]. Furthermore, when calorie loads exceed the glucose uptake capacity of skeletal muscle, the circulating glucose mostly returns to the liver, triggering hepatic *de novo* lipogenesis[3], which causes ectopic fat deposition in the liver and other tissues, further exacerbating insulin resistance[13]. Therefore, impaired glucose uptake in skeletal muscle has been considered as a major culprit of type 2 diabetes[14-16] and targeted as a therapeutic strategy against insulin resistance[17,18].

A recent study suggests that microbial products derived from phenolic acids may increase glucose uptake in skeletal muscle under insulin-stimulated condition[19]. Microbiota-produced phenolic metabolites are derived from ferulic acid, resveratrol, and berries. The ferulic acid-derived metabolites, ferulic acid 4-O-sulfate and dihydroferulic acid 4-O-sulfate, and the resveratrol-derived metabolites, *trans*-resveratrol 4'-O-glucuronide and *trans*-resveratrol 3-O-sulfate, increased 2-deoxy-D-[1-¹⁴C(U)]-glucose uptake in LHCN-M2 human skeletal muscle cells[19]. Isovanillic acid 3-O-sulfate, which is primarily derived from berries, increased glucose uptake in myotubes through GLUT4-PI3K-AKT-dependent mechanisms and stimulated dose-dependent glucose uptake[19]. On the other hands, a study has been shown that bacterial-derived metabolite-complex can decrease glucose uptake, though the exact composition of the complex is not defined[20]. Gut bacteria-derived extracellular vesicles (EVs), which are phospholipid spherical bilayer, are ubiquitously produced by gram-negative bacteria [20]. Especially, *Pseudomonas panacis*-derived EVs increasing in a high-fat diet (HFD)-fed mice compared to regular chow-fed mice as well as gut microbe-derived EVs from HFD-fed mice stools induced insulin resistance, including impairment of insulin signaling both *in vitro* and *in vivo*, and impairment of glucose uptake by decreasing insulin-dependent GLUT4 translocation, both in myotubes and adipocytes [20].

Insulin-independent glucose uptake is also activated by microbial metabolites. Activation of AMP-activated protein kinase (AMPK) in response to exercise regulates the translocation of GLUT4 storage vesicles and promotes insulin-independent glucose uptake[21]. In particular, 5-(3,5-dihydroxyphenyl)- γ -valerolactone has been shown to increase GLUT4 translocation *via* activation of AMPK through an insulin-independent pathway in skeletal muscle both *in vitro* and *in vivo*[22]. The antidiabetic green tea

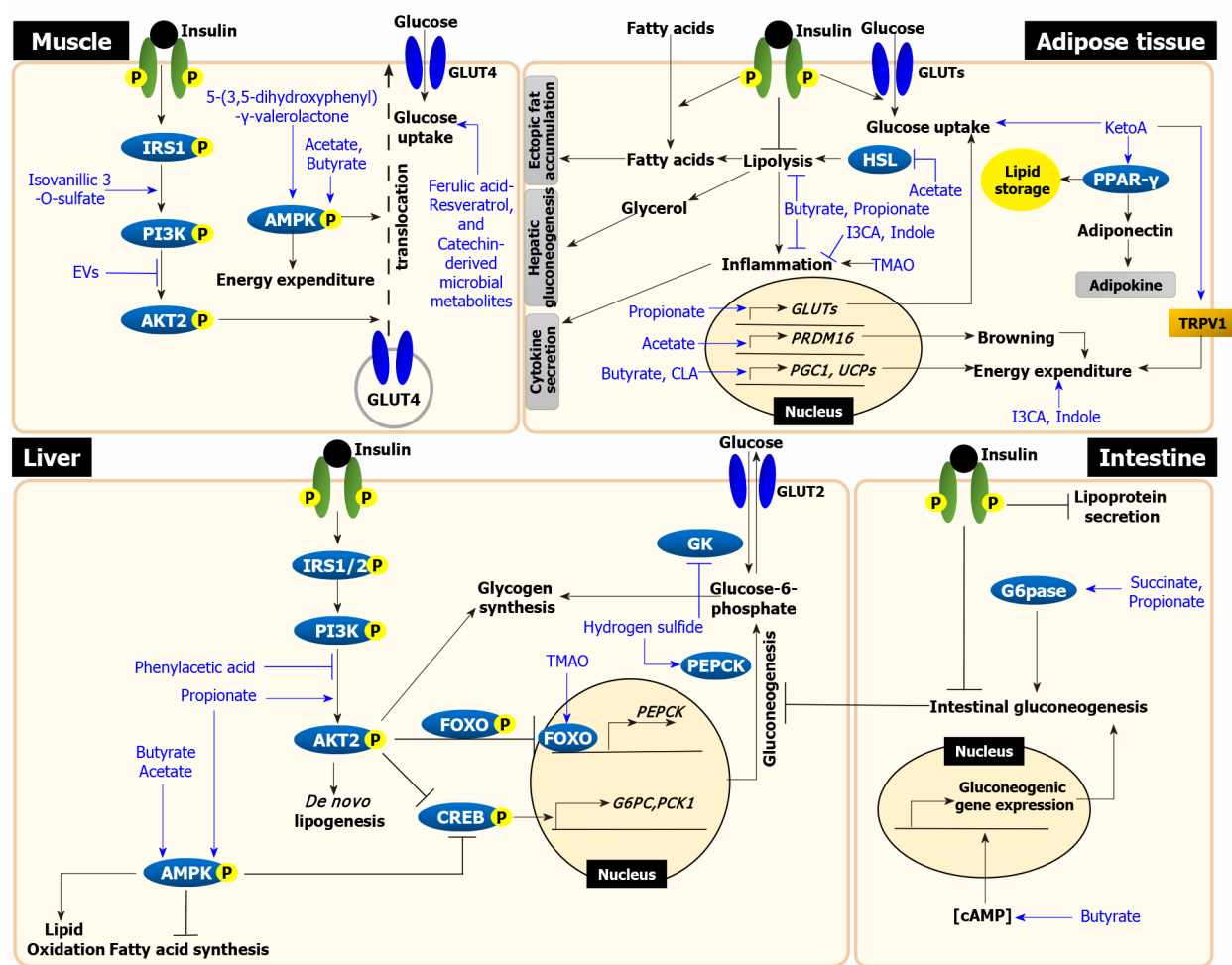


Figure 1 The mechanisms linking microbial metabolites to insulin resistance. In skeletal muscle, insulin stimulates glucose uptake by translocating glucose transporter (GLUT) 4 via insulin receptor substrate (IRS)-phosphoinositide-3-kinase (PI3K)-AKT signaling. Isovannillic 3-O-sulfate increases glucose uptake by activating PI3K-AKT pathway. Gut bacteria-derived extracellular vesicles (EVs) decrease glucose uptake by inhibiting AKT phosphorylation. Glucose uptake is also increased via AMP-activated protein kinase (AMPK) activation, insulin-independent. 5-(3,5-dihydroxyphenyl)- γ -valerolactone activates AMPK phosphorylation, which enhances glucose uptake. Although mechanisms have been unknown, other ferulic acid, resveratrol, and catechin-derived microbial metabolites also enhance glucose uptake (left upper panel). In liver, insulin activates glycogen synthesis and *de novo* lipogenesis and suppresses gluconeogenesis via IRS-PI3K-AKT signaling. Propionate increases the phosphorylation of both AKT and AMPK, which suppresses gluconeogenesis. Hydrogen sulfide stimulates gluconeogenesis via phosphoenolpyruvate carboxykinase activation and reduces glycogen synthesis via the inhibition of glucokinase activity. Trimethylamine N-oxide (TMAO) increases gluconeogenesis via PKR-like ER kinase-FOXO1 pathway. Phenylacetic acid inhibits AKT phosphorylation. All short chain fatty acids (SCFAs), including acetate, propionate, and butyrate, activate AMPK phosphorylation, which lead to decrease lipid accumulation (left lower panel). In adipose tissue, insulin stimulates glucose and fatty acid uptake and suppress lipolysis. Failure to suppress lipolysis in insulin-resistant adipose tissue increases circulating free fatty acids and glycerol, which leads to an increase in ectopic fat accumulation in the liver and muscle and stimulates hepatic gluconeogenesis. 10-oxo-12(Z)-octadecenoic acid (KetoA) increases insulin-stimulated glucose uptake and energy expenditure via TRPV2 activation. KetoA also increases the production and secretion of adiponectin via peroxisome proliferator-activated receptor- γ activation. TMAO increases inflammation in adipocyte. Indole and I3CA have anti-inflammatory effects. Conjugated linoleic acid enhances energy expenditure by increasing the expression of uncoupling proteins (UCPs) genes. All SCFAs inhibit lipolysis. Acetate inhibits lipolysis by suppressing HSL and stimulates also browning by increasing the expression of browning-related genes. Butyrate and propionate attenuate inflammation. Propionate increases glucose uptake by increasing GLUT4 expression. Butyrate enhances energy expenditure by upregulating PPAR- γ coactivator 1 and UCPs genes (right upper panel). The intestine, as discussed in this review, is an organ that actively interacts with gut bacteria and accumulates microbial metabolites. Intestinal lipoprotein secretion and gluconeogenesis are suppressed by insulin. In intestine, propionate and succinate act as gluconeogenic substrate, which activate gluconeogenesis via G6Pase activation. Butyrate increases cyclic adenosine monophosphate levels, which upregulates the expression of gluconeogenic genes and increases gluconeogenesis. Through this mechanisms, increased intestinal gluconeogenesis suppresses hepatic gluconeogenesis (right lower panel). Black lines represent insulin resistance-related events and blue lines represent action of metabolites. Grey boxes represent the effects of adipose tissue on other tissues. EVs: Extracellular vesicles; PEPCK: Phosphoenolpyruvate carboxykinase; GK: Glucokinase; TMAO: Trimethylamine N-oxide; PERK: PKR-like ER kinase; FOXO1: Forkhead box protein O1; cAMP: Cyclic adenosine monophosphate; CREB: cAMP-response element binding protein; G6PC: Glucose 6-phosphatase catalytic subunit; PCK1: Phosphoenolpyruvate carboxykinase 1; TRPV1: Transient receptor potential vanilloid 1; PPAR: Peroxisome proliferator-activated receptor; I3CA: Indole-3-carboxylic acid; CLA: Conjugated linoleic acid; HSL: Hormone-sensitive lipase; PRDM16: PR domain containing 16; PGC1: Peroxisome proliferator-activated receptor- γ coactivator 1; G6Pase: Glucose 6-phosphatase.

catechin (-)-epigallocatechin gallate (EGCG) is further degraded by *Flavonifractor plautii*[23], and several gut bacteria-derived EGCG metabolites, including 5-(3,5-dihydroxyphenyl)- γ -valerolactone, 4-hydroxy-5-(3,4,5-trihydroxyphenyl)valeric acid,

5-(3,4,5-trihydroxyphenyl)- γ -valerolactone, and 5-(3-hydroxyphenyl) valeric acid, have been shown to promote 2-deoxy-glucose uptake in myotubes *in vitro*[22]. It has been reported that *Flavonifractor plautii* was decreased in fecal microbiota of subjects with mild fasting hyperglycemia[24].

Liver

The liver is a central organ that coordinates whole-body metabolism, including carbohydrate, lipid, and protein metabolism. The liver is responsible for gluconeogenesis, glycogenolysis, glycogen synthesis, and *de novo* lipogenesis[1]. In contrast to skeletal muscle, hepatic glucose uptake is not regulated by insulin but blood glucose levels because GLUT2, a transporter with a high K_M for glucose, is abundantly expressed in the liver and not translocated by insulin stimulation[25]. Rather than regulating the glucose uptake, in the liver, insulin suppresses hepatic glucose production by reducing the transcription of gluconeogenic enzymes[26,27] and induces a shift from net glucose production to net glucose storage by simultaneous regulation of glycogenolysis and glycogen synthesis[2]. However, in an insulin-resistant state, these regulations are not controlled by insulin, and the non-suppressed hepatic glucose production under insulin stimulated condition has been considered as a marker for hepatic insulin resistance[1,28]. It has been reported that propionate, a gut microbial product derived from carbohydrate fermentation, regulates hepatic gluconeogenesis under insulin stimulated condition[29]. Previously, stable isotope studies in both humans and animals have showed that propionate is used as a gluconeogenic substrate in the liver rather than being directly oxidized[30,31]. Recently, it was reported that propionate effectively suppresses hepatic glucose production in both presence and absence of long chain fatty acid by increasing the expression of gluconeogenesis-related genes, including *G6PC* and *PCK1*, via the G protein-coupled receptor (GPCR) 43-mediated AMPK signaling pathway under insulin-stimulated condition as well as increases AKT phosphorylation in HepG2 hepatocyte[29]. In addition to insulin-stimulated condition, it has been reported that gut bacterial metabolites regulate hepatic glucose production under non-insulin stimulated basal condition [32, 33]. Hydrogen sulfide, a product of protein fermentation, is not only generated in the body but also produced by sulfate-reducing bacteria, including *Desulfovibrio*, *Desulfobacter*, *Desulfomonas*, and *Desulfobulbus*, in the colon[32,34] and affects the basal hepatic glucose production. Under basal condition, this metabolite impairs glucose homeostasis by stimulating gluconeogenesis via increased phosphoenolpyruvate carboxykinase activity and decreased glucokinase by reducing glycogen synthesis in HepG2 human hepatoma cells[32]. In type 2 diabetes patients, it has been reported that the plasma hydrogen sulfide levels were reduced compared to healthy subjects[35,36], suggesting clinical association of microbial metabolites in hyperglycemia. Trimethylamine N-oxide (TMAO), which is known as a gut bacterial metabolite derived from choline, is converted by hepatic enzymes from trimethylamine, a choline-derived microbial metabolite, in liver[37]. The production of TMAO is completely suppressed in both antibiotics-treated humans and mice but the plasma of TMAO levels return to normal after the withdrawal of the antibiotics[38,39]. It has been reported that TMAO increases with insulin resistance in both humans and animals[40-42]. In mice, TMAO treatment promoted glucose intolerance, while a reduction of TMAO prevented glucose intolerance[33]. Under basal condition, the treatment of TMAO in mice activated PKR-like ER kinase and increased gluconeogenic gene expression, including *G6pc* and *Pck1*, via the forkhead box protein O1 transcription factor, which promoted hyperglycemia[33,43].

In addition to glucose metabolism, insulin also controls lipid metabolism in the liver. Since insulin normally promotes net hepatic *de novo* lipogenesis, one might expect decreased *de novo* lipogenesis in an insulin-resistant state; however, hepatic insulin resistance is highly associated with hepatic steatosis[1,3], and *de novo* lipogenesis is consistently elevated in insulin-resistant liver tissue[3]. This phenomenon has been termed “selective hepatic insulin resistance,” as glucose metabolism is affected by insulin resistance but lipid metabolism is not affected[44]. The increased *de novo* lipogenesis could be partly accounted by hyperinsulinemia, but still there are selective insulin resistance between glucose and lipid when considers the action of insulin *per se*[3,4]. Nevertheless, microbial metabolites can regulate the hepatic lipid metabolism. Phenylacetic acid is a microbial metabolite derived from aromatic compounds and produced by *Bacteroides spp.*, which have aromatic amino acids fermentative activities[45]. Plasma phenylacetic acid positively correlates with the nonalcoholic fatty liver disease activity score in humans[9,46]. Phenylacetic acid induced the accumulation of hepatic triglycerides both in cellular and animal studies [46]. The metabolite also reduced insulin-induced AKT phosphorylation in human

primary hepatocytes[46]. In contrast, short chain fatty acids (SCFAs), including acetate, propionate, and butyrate, decreased hepatic lipid accumulation. Administration of all three SCFAs in HFD-fed mice decreased not only total body fat content, without a change in food intake, but also the expression of genes related to hepatic lipogenesis and fatty acid synthase[47]. In addition, hepatic lipid oxidation capacity in SCFA-fed mice was increased *via* upregulation of mitochondrial uncoupling protein (UCP) 2 expression and activation of AMPK[47-49]. The SCFA acetate inhibited fatty acid synthesis in the liver *via* activation of AMPK. Oral administration of acetate stimulated the phosphorylation of AMPK, which inactivates carbohydrate-responsive element-binding protein[50], and in turn modulated the transcription of lipogenic genes in the liver[51]. Acetate also suppressed the increases in whole-body fat mass and hepatic lipid accumulation by increasing the expression of genes encoding peroxisome proliferator-activated receptor (PPAR) α and fatty acid oxidation-related proteins through AMPK α 2 in the liver[52]. In mice, acetate treatment improved liver mitochondrial function by increasing the number of cristae, the location of the electron transport chain, per mitochondria, and the expression of complexes III, IV, and V[53]. Another SCFA, butyrate, increased mitochondrial mass and area and improved fatty acid oxidation in the liver of HFD-fed mice[49].

Adipose tissue

Adipose tissue is an energy storage organ[5]. In adipose tissue, insulin-stimulated glucose uptake also occurs *via* GLUT4 translocation, which is greatly reduced in insulin resistant condition, such as obesity and type 2 diabetes[54]. A linoleic acid-derived fatty acid generated by gut lactic acid bacteria, 10-oxo-12(Z)-octadecenoic acid (KetoA), induced adipocyte differentiation *via* activation of PPAR γ , and increased the production of adiponectin and insulin-stimulated glucose uptake in 3T3-L1 murine adipocytes[55]. However, physiologically, adipose tissue is not quantitatively significant in insulin-stimulated glucose disposal because it accounts for < 5% of blood glucose uptake in our body[16]. Rather than glucose metabolism, insulin may have more critical roles in lipid metabolism of adipose tissues, thus the suppression of lipolysis is an important function of insulin in adipose tissue[4]. Failure to suppress lipolysis in insulin-resistant adipose tissue increases circulating free fatty acids and glycerol[15,56], and affects in hepatic glucose production[1]. These increased levels of circulating free fatty acids lead to an increase in ectopic fat accumulation in the liver and muscle, further exacerbating insulin resistance[15]. In addition, the glycerol released from adipose tissue serves as a gluconeogenic substrate and stimulates hepatic gluconeogenesis[1]. Suppression of lipolysis also reduces the levels of acetyl-CoA, an allosteric activator of pyruvate carboxylase, decreases pyruvate carboxylase activity[57]. As a result, gluconeogenic flux, involving glycerol and acetyl-CoA, is diminished, resulting in decreased hepatic gluconeogenesis[57]. Therefore, the regulation of lipolysis in adipose tissue is considered a therapeutic strategy against insulin resistance[58]. In the SCFAs, it has been reported both acetate and propionate stimulate adipogenesis and inhibit lipolysis *via* activation of GPCR43 but not GPCR41 [59,60]. Acetate might inhibit basal and beta-adrenergic receptor-mediated intracellular lipolysis *via* attenuation of hormone-sensitive lipase phosphorylation in human adipose tissue-derived adipocytes and lead to a reduction in non-esterified fatty acid release[61]. Injection of acetate into fasted mice led to decreased plasma free fatty acid levels *via* activation of GPCR43[60].

Adipose tissue also functions as an endocrine organ and releases adipokines, lipids, and cytokines, which regulates whole-body metabolism[62]. Adipose tissue can secrete molecules associated with improved insulin sensitivity, including adiponectin and branched fatty acid esters of hydroxyl fatty acids[63]. Chronic low-grade inflammation occurs in obese individuals with insulin resistance, which is mainly induced by adipose tissue inflammation[64]. Inflammation of adipose tissue is caused by macrophage infiltration, which impairs the insulin sensitivity of insulin target organs, resulting in insulin resistance[65]. TMAO, a microbial metabolite derived from choline, promoted adipose tissue inflammation in HFD-fed mice by increasing mRNA and serum levels of monocyte chemoattractant protein-1 (MCP-1), the proinflammatory cytokine, and decreasing mRNA and serum levels of interleukin (IL)-10, the anti-inflammatory cytokine, in adipose tissue[43]. Conversely, the SCFAs propionate and butyrate improved adipose tissue inflammation. Propionate may have a directly beneficial effect on adipose tissue in overweight subjects, as it reduced the mRNA expression and secretion of inflammatory cytokines and increased the mRNA expression of genes involved in lipogenesis (*e.g.*, *LPL*, *SREBP1c*) and glucose uptake (*e.g.*, *GLUT4*)[66]. Butyrate suppressed lipolysis and inflammatory responses, including the upregulation of tumor necrosis factor- α , MCP-1, and IL-6, which are generated by

the interaction of adipocytes and macrophages [67]. It has been reported that gut bacterial metabolites derived from protein fermentation have anti-inflammatory effects in adipose tissue. Indole-3-carboxylic acid and indole, a tryptophan-derived microbial metabolites, are decreased in the cecal contents of HFD-fed mice compared to regular chow-fed mice[10]. These metabolites increased energy expenditure and improved insulin sensitivity by decreasing the expression of the *microRNA miR-181*, which is upregulated in HFD feeding and increases white adipose tissue (WAT) inflammation[10].

Brown adipose tissue and whole body energy expenditure

Unlike WAT, because brown adipose tissue (BAT) is responsible for energy expenditure by burning fatty acids to produce heat, it is an important organ that effects on whole body energy metabolism[68]. Similarly increasing beige adipocytes in WAT, a process termed “browning,” results in increased heat production and energy expenditure[69]. Therefore, enhanced BAT activity and browning of WAT are important for energy expenditure and are thought to influence insulin sensitivity[68, 69]. It has been reported that gut bacterial metabolites derived from carbohydrates and fatty acids increase energy expenditure *via* browning of WAT and/or enhancing the function of BAT. SCFAs, including acetate, propionate, and butyrate, which are products of dietary fiber fermentation by gut bacteria. Acetate is mainly produced by *Bifidobacteria* and *Lactobacillus* and propionate is largely produced by *Bacteroides* and *Veillonella*, such as *Bacteroides eggerthii*, *Bacteroides fragilis*, and *Veillonella parvula*[70,71]. Butyrate is mostly produced by anaerobic bacteria, including *Faecalibacterium prausnitzii*, and *Eubacterium rectale*[72]. Acetate enhanced beige fat differentiation of white adipocytes *in vitro*[73]. Acetate and butyrate promoted browning in adipocytes [53,74]. In obese diabetic mice, acetate also induced browning of adipocytes by increasing thermogenesis-related gene expression, altered adipocyte morphology, and increased the thermogenic capacity of adipose tissue, independent of BAT, in HFD-fed mice[53,73]. Butyrate exerted an anti-obesity effect in animal models by strengthening the function of BAT. This anti-obesity effect occurs by increasing in energy expenditure and fat oxidation through upregulation of the expression of thermogenesis-related genes in BAT, such as PPAR- γ coactivator 1- α (PGC1 α) and UCP1[48, 74]. All SCFAs stimulated lipid oxidation by activating AMPK in the liver and adipose tissue[47]. Similarly, in skeletal muscle, acetate improved oxygen consumption by increasing the expression of lipid oxidation-related genes and AMPK activity in animal models[75]. Butyrate increased oxygen consumption and energy expenditure both *in vitro* and *in vivo*. These effects are caused by activation of AMPK and inhibition of histone deacetylases, which activate PGC1 α and subsequently increase the expression of PPAR δ , thus promoting fatty acid oxidation and increasing the proportion of type I muscle fibers, which are characterized by their high oxidative capacity[48]. In contrast to animal models, treatment of both lean and metabolic syndrome subjects with butyrate had no effect on BAT function[76], and open to debate over the single treatment. However, infusion of SCFA mixtures of acetate, propionate, and butyrate increased fat oxidation and whole-body energy expenditure in overweight/obese men[77,78]. These effects were observed following treatment with each SCFA alone as well as mixtures of the SCFAs. Propionate increased whole-body energy expenditure and fat oxidation in healthy and overweight/obese humans [79]. These findings suggested that SCFAs affect whole-body energy expenditure through a combination of mechanisms in different tissues, including skeletal muscle, the liver, and adipose tissue.

There are several studies show that fatty acid-derived microbial metabolites effect on energy expenditure. KetoA, a linoleic acid-derived microbial metabolite, has been suggested as the regulator of host energy metabolism. The anti-obesity effect of KetoA is shown *via* the activation of transient receptor potential vanilloid 1 (TRPV1), a member of the TRPV channel family, which has been reported to be important for the regulation of energy metabolism in adipocytes[80,81]. KetoA-induced TRPV1 activation enhanced energy expenditure by increasing the function of both BAT and WAT in diabetic mice[81]. Conjugated linoleic acid (CLA) is also mainly produced from linoleic acid by lactic acid bacteria, and enhances energy expenditure *via* increase in the expression of UCPs genes in adipose tissue[82,83]. Mice fed CLA-producing bacteria, *Lactobacillus rhamnosus* PL60, are prevented from diet-induced obesity and hepatic steatosis[84].

Intestine

The small intestine takes up glucose from the intestinal lumen mainly through sodium-glucose cotransporter 1 and transports glucose from enterocytes to the blood

via GLUT2[85]. Although it has been reported that insulin inhibits the translocation of GLUT2 from the basolateral surface to the apical epithelial membrane, the role of insulin in intestinal glucose uptake is unclear[85,86]. Insulin signaling has been implicated in both increased and decreased glucose uptake from the intestinal lumen to the enterocytes in both humans and *in vitro* studies[87]. Beside the glucose uptake, insulin's action on lipid metabolism and gluconeogenesis seems to be well established in intestine. Insulin modulates lipoprotein metabolism in the intestine and suppresses lipoprotein secretion[86]. Production of apolipoproteinB48-containing chylomicrons by the small intestine increases insulin resistance[86,88]. Like liver, the intestine shows gluconeogenic capacity. Intestinal glucose production is suppressed by insulin and increased in insulinopenic states, such as a 48-h fasting and type 1 diabetes[89,90]. In a postprandial state, intestinal gluconeogenesis (IGN) accounts for about 5%-7% of the total endogenous glucose production[91-93]. A protein-rich diet increases the expression of genes involved in IGN in the intestine and the regulatory enzymes in gluconeogenesis and glutaminase[94]. In intestine, the peptides digested from protein-rich diet act on μ -opioid receptors presenting in the portal vein nerves[94], which signals to the brain and releases of the neuromediator vasoactive intestinal peptide from brain during the postprandial period[95]. This neuromediator activates adenylate cyclase and increases cAMP levels, which induces the expression of IGN-related genes [95]. The IGN-related enzymes are progressively induced during the postprandial period, and the amount of enzyme is maintained during the post-absorptive period[94, 96]. In addition, because protein-rich diets provide major IGN substrates, including glutamine and glutamate, these substrates can be utilized by IGN induced during the post-absorptive period[97]. It was recently reported that IGN protects against diabetes and obesity by suppressing hepatic gluconeogenesis and positively regulating glucose homeostasis[91,92]. Gastric bypass surgery also has been reported to increase IGN and suppress hepatic gluconeogenesis in diabetic animal model[93,98].

It has been reported that IGN is induced by the SCFAs and succinate, the gut microbial metabolites derived from carbohydrate fermentation[91,92]. The SCFA propionate, as a gluconeogenic substrate, activated G6Pase activity and increased IGN gene expression *via* vasoactive intestinal peptide released from brain through a gut-brain neural circuit involving the free fatty acid receptor 3-dependent stimulation [91, 95]. Propionate showed the strongest capacity to induce intestinal glucose production among SCFAs[91]. Another SCFA, butyrate increased the levels of ATP, a substrate of adenylate cyclase, which promoted the production of cyclic AMP[91]. Cyclic AMP functions as an intracellular messenger that stimulates the expression of genes involved in gluconeogenesis[99]. Through this mechanism, butyrate promoted gluconeogenesis in enterocytes[91]. Microbial-derived succinate not only showed an anti-obesity effect but also improved glucose tolerance and insulin sensitivity. Succinate functioned as a gluconeogenic substrate such as propionate, and it was shown to promote activation of gluconeogenesis in the intestine of high-fat and high-sucrose diet-fed mice[92]. In addition, succinate-fed wild-type mice showed a decreased capacity for hepatic glucose production, and this suppression of hepatic gluconeogenesis was absent in succinate-fed *G6pc* intestinal-specific knockout mice[92]. In humans, it has been reported that succinate-producing bacteria, including *Bacteroidaceae* and *Prevotella*, were found to be increased in fecal samples of patients with non-alcoholic steatohepatitis[92,100].

CONCLUSION

Since the association between microbiome and metabolic diseases in the last 20 years has been increasingly revealed, microbial metabolites are considered to be the link between microbiome and metabolic diseases. This review summarized the role of microbial metabolites in the major mechanisms representing insulin resistance in each tissue. Through this, in addition to SCFAs, which has been studied a lot in the past, recent studies have found some candidates that protein-derived (*e.g.*, hydrogen sulfide, Indole-3-carboxylic acid, and phenylacetic acid) and lipid-derived microbial metabolites (*e.g.*, KetoA and CLA) can play a role in the pathogenesis of insulin resistance. However, metabolites by gut bacteria are highly diverse depending on intestinal environments (*e.g.*, dietary substrates, host enzyme, acidity, temperature, and antibiotics), yet only limited number of metabolites have been identified and functionally studied in metabolic diseases. Indeed, according to Human Microbiome Database, over 100 thousand of metabolites are existed in our body, but only hundreds are counted as bacterial-specific (<https://hmdb.ca/statistics>).

What makes this even more challengeable is the complex etiology of insulin resistance. In glucose and lipid metabolism, each organ is highly interrelated. Muscle insulin resistance can divert ingested glucose into the liver, and increase hepatic de novo lipogenesis and gluconeogenesis. Adipose tissue insulin resistance can release lipogenic and gluconeogenic substrates to liver as well as intestinal IGLN reversely controls the hepatic gluconeogenesis. In order to develop bacterial metabolites as a therapeutic agent for insulin resistance in humans, not only clarifying the exact mechanism of action for which stage of insulin resistance, but also understanding metabolic complexities between multiple organs should be conducted in parallel. Nevertheless, insulin resistance is a common prerequisite for various metabolic diseases, the discovery of metabolites that specifically act on insulin resistance is a strategy to overcome metabolic diseases in terms of more fundamental etiology and early prevention, and more research should be conducted.

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