**Name of Journal:** *World Journal of Diabetes*

**Manuscript NO:** 63858

**Manuscript Type:** REVIEW

**Mechanisms linking gut microbial metabolites to insulin resistance**

Jang HR *et al*. Gut microbial metabolites and insulin resistance

Hye Rim Jang, Hui-Young Lee

**Hye Rim Jang, Hui-Young Lee,** Laboratory of Mitochondrial and Metabolic Diseases, Department of Health Sciences and Technology, GAIHST, Gachon University, Incheon 21999, South Korea

**Hui-Young Lee,** Korea Mouse Metabolic Phenotyping Center, Lee Gil Ya Cancer and Diabetes Institute, Gachon University, Incheon 21999, South Korea

**Hui-Young Lee,** Division of Molecular Medicine, Department of Medicine, Gachon University College of Medicine, Incheon 21936, South Korea

**Author contributions:** Jang HR and Lee HY wrote the manuscript; all authors have read and approved the final manuscript.

**Supported by** National Research Foundation Funded by the Korean Ministry of Science, No. NRF-2018M3A9F3056405 and No. NRF-2020R1A2B5B01002789.

**Corresponding author: Hui-Young Lee, DVM, PhD, Associate Professor,** Laboratory of Mitochondrial and Metabolic Diseases, Department of Health Sciences and Technology, GAIHST, Gachon University, 155, Gaetbeol-ro, Yeonsu-gu, Incheon 21999, South Korea. hylee@gachon.ac.kr

**Received:** February 10, 2021

**Revised:** March 23, 2021

**Accepted:** May 20, 2021

**Published online:** June 15, 2021

**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

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation：** Jang HR, Lee HY. Mechanisms linking gut microbial metabolites to insulin resistance. *World J Diabetes* 2021; 12(6): 730-744

**URL:** <https://www.wjgnet.com/1948-9358/full/v12/i6/730.htm>

**DOI:** https://dx.doi.org/10.4239/wjd.v12.i6.730

**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.

**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 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 micecompared 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 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 maker 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-mediataed 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 α2 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 PPARγ, 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 (PGC1α) 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 PGC1α and subsequently increase the expression of PPARδ, 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-opioide 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 exited 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 intestinal IGN 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.

**REFERENCES**

1 **Petersen MC**, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. *Physiol Rev* 2018; **98**: 2133-2223 [PMID: 30067154 DOI: 10.1152/physrev.00063.2017]

2 **Samuel VT**, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. *Cell* 2012; **148**: 852-871 [PMID: 22385956 DOI: 10.1016/j.cell.2012.02.017]

3 **Samuel VT**, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. *J Clin Invest* 2016; **126**: 12-22 [PMID: 26727229 DOI: 10.1172/JCI77812]

4 **Erion DM**, Park HJ, Lee HY. The role of lipids in the pathogenesis and treatment of type 2 diabetes and associated co-morbidities. *BMB Rep* 2016; **49**: 139-148 [PMID: 26728273 DOI: 10.5483/bmbrep.2016.49.3.268]

5 **Gesta S**, Tseng YH, Kahn CR. Developmental origin of fat: tracking obesity to its source. *Cell* 2007; **131**: 242-256 [PMID: 17956727 DOI: 10.1016/j.cell.2007.10.004]

6 **Lee Y**, Lee HY. Revisiting the Bacterial Phylum Composition in Metabolic Diseases Focused on Host Energy Metabolism. *Diabetes Metab J* 2020; **44**: 658-667 [PMID: 32662252 DOI: 10.4093/dmj.2019.0220]

7 **Schroeder BO**, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. *Nat Med* 2016; **22**: 1079-1089 [PMID: 27711063 DOI: 10.1038/nm.4185]

8 **Chen MX**, Wang SY, Kuo CH, Tsai IL. Metabolome analysis for investigating host-gut microbiota interactions. *J Formos Med Assoc* 2019; **118 Suppl 1**: S10-S22 [PMID: 30269936 DOI: 10.1016/j.jfma.2018.09.007]

9 **Wikoff WR**, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC, Siuzdak G. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proc Natl Acad Sci U S A* 2009; **106**: 3698-3703 [PMID: 19234110 DOI: 10.1073/pnas.0812874106]

10 **Virtue AT**, McCright SJ, Wright JM, Jimenez MT, Mowel WK, Kotzin JJ, Joannas L, Basavappa MG, Spencer SP, Clark ML, Eisennagel SH, Williams A, Levy M, Manne S, Henrickson SE, Wherry EJ, Thaiss CA, Elinav E, Henao-Mejia J. The gut microbiota regulates white adipose tissue inflammation and obesity *via* a family of microRNAs. *Sci Transl Med* 2019; **11** [PMID: 31189717 DOI: 10.1126/scitranslmed.aav1892]

11 **Baron AD**, Brechtel G, Wallace P, Edelman SV. Rates and tissue sites of non-insulin- and insulin-mediated glucose uptake in humans. *Am J Physiol* 1988; **255**: E769-E774 [PMID: 3059816 DOI: 10.1152/ajpendo.1988.255.6.E769]

12 **Zorzano A**, Muñoz P, Camps M, Mora C, Testar X, Palacín M. Insulin-induced redistribution of GLUT4 glucose carriers in the muscle fiber. In search of GLUT4 trafficking pathways. *Diabetes* 1996; **45 Suppl 1**: S70-S81 [PMID: 8529804 DOI: 10.2337/diab.45.1.s70]

13 **Perry RJ**, Samuel VT, Petersen KF, Shulman GI. The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. *Nature* 2014; **510**: 84-91 [PMID: 24899308 DOI: 10.1038/nature13478]

14 **DeFronzo RA**, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care* 2009; **32 Suppl 2**: S157-S163 [PMID: 19875544 DOI: 10.2337/dc09-S302]

15 **Shulman GI**. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med* 2014; **371**: 1131-1141 [PMID: 25229917 DOI: 10.1056/NEJMra1011035]

16 **Kowalski GM**, Bruce CR. The regulation of glucose metabolism: implications and considerations for the assessment of glucose homeostasis in rodents. *Am J Physiol Endocrinol Metab* 2014; **307**: E859-E871 [PMID: 25205823 DOI: 10.1152/ajpendo.00165.2014]

17 **Kalinovich A**, Dehvari N, Åslund A, van Beek S, Halleskog C, Olsen J, Forsberg E, Zacharewicz E, Schaart G, Rinde M, Sandström A, Berlin R, Östenson CG, Hoeks J, Bengtsson T. Treatment with a β-2-adrenoceptor agonist stimulates glucose uptake in skeletal muscle and improves glucose homeostasis, insulin resistance and hepatic steatosis in mice with diet-induced obesity. *Diabetologia* 2020; **63**: 1603-1615 [PMID: 32472192 DOI: 10.1007/s00125-020-05171-y]

18 **Vieira R**, Souto SB, Sánchez-López E, Machado AL, Severino P, Jose S, Santini A, Fortuna A, García ML, Silva AM, Souto EB. Sugar-Lowering Drugs for Type 2 Diabetes Mellitus and Metabolic Syndrome-Review of Classical and New Compounds: Part-I. *Pharmaceuticals (Basel)* 2019; **12** [PMID: 31658729 DOI: 10.3390/ph12040152]

19 **Houghton MJ**, Kerimi A, Mouly V, Tumova S, Williamson G. Gut microbiome catabolites as novel modulators of muscle cell glucose metabolism. *FASEB J* 2019; **33**: 1887-1898 [PMID: 30183376 DOI: 10.1096/fj.201801209R]

20 **Choi Y**, Kwon Y, Kim DK, Jeon J, Jang SC, Wang T, Ban M, Kim MH, Jeon SG, Kim MS, Choi CS, Jee YK, Gho YS, Ryu SH, Kim YK. Gut microbe-derived extracellular vesicles induce insulin resistance, thereby impairing glucose metabolism in skeletal muscle. *Sci Rep* 2015; **5**: 15878 [PMID: 26510393 DOI: 10.1038/srep15878]

21 **Steinberg GR**, Kemp BE. AMPK in Health and Disease. *Physiol Rev* 2009; **89**: 1025-1078 [PMID: 19584320 DOI: 10.1152/physrev.00011.2008]

22 **Takagaki A**, Yoshioka Y, Yamashita Y, Nagano T, Ikeda M, Hara-Terawaki A, Seto R, Ashida H. Effects of Microbial Metabolites of (-)-Epigallocatechin Gallate on Glucose Uptake in L6 Skeletal Muscle Cell and Glucose Tolerance in ICR Mice. *Biol Pharm Bull* 2019; **42**: 212-221 [PMID: 30713253 DOI: 10.1248/bpb.b18-00612]

23 **Takagaki A**, Kato Y, Nanjo F. Isolation and characterization of rat intestinal bacteria involved in biotransformation of (-)-epigallocatechin. *Arch Microbiol* 2014; **196**: 681-695 [PMID: 24947740 DOI: 10.1007/s00203-014-1006-y]

24 **Wu H**, Tremaroli V, Schmidt C, Lundqvist A, Olsson LM, Krämer M, Gummesson A, Perkins R, Bergström G, Bäckhed F. The Gut Microbiota in Prediabetes and Diabetes: A Population-Based Cross-Sectional Study. *Cell Metab* 2020; **32**: 379-390.e3 [PMID: 32652044 DOI: 10.1016/j.cmet.2020.06.011]

25 **Thorens B**. GLUT2, glucose sensing and glucose homeostasis. *Diabetologia* 2015; **58**: 221-232 [PMID: 25421524 DOI: 10.1007/s00125-014-3451-1]

26 **Liu Y**, Dentin R, Chen D, Hedrick S, Ravnskjaer K, Schenk S, Milne J, Meyers DJ, Cole P, Yates J 3rd, Olefsky J, Guarente L, Montminy M. A fasting inducible switch modulates gluconeogenesis *via* activator/coactivator exchange. *Nature* 2008; **456**: 269-273 [PMID: 18849969 DOI: 10.1038/nature07349]

27 **Puigserver P**, Rhee J, Donovan J, Walkey CJ, Yoon JC, Oriente F, Kitamura Y, Altomonte J, Dong H, Accili D, Spiegelman BM. Insulin-regulated hepatic gluconeogenesis through FOXO1-PGC-1alpha interaction. *Nature* 2003; **423**: 550-555 [PMID: 12754525 DOI: 10.1038/nature01667]

28 **Lee HY**, Birkenfeld AL, Jornayvaz FR, Jurczak MJ, Kanda S, Popov V, Frederick DW, Zhang D, Guigni B, Bharadwaj KG, Choi CS, Goldberg IJ, Park JH, Petersen KF, Samuel VT, Shulman GI. Apolipoprotein CIII overexpressing mice are predisposed to diet-induced hepatic steatosis and hepatic insulin resistance. *Hepatology* 2011; **54**: 1650-1660 [PMID: 21793029 DOI: 10.1002/hep.24571]

29 **Yoshida H**, Ishii M, Akagawa M. Propionate suppresses hepatic gluconeogenesis *via* GPR43/AMPK signaling pathway. *Arch Biochem Biophys* 2019; **672**: 108057 [PMID: 31356781 DOI: 10.1016/j.abb.2019.07.022]

30 **den Besten G**, Lange K, Havinga R, van Dijk TH, Gerding A, van Eunen K, Müller M, Groen AK, Hooiveld GJ, Bakker BM, Reijngoud DJ. Gut-derived short-chain fatty acids are vividly assimilated into host carbohydrates and lipids. *Am J Physiol Gastrointest Liver Physiol* 2013; **305**: G900-G910 [PMID: 24136789 DOI: 10.1152/ajpgi.00265.2013]

31 **Boets E**, Gomand SV, Deroover L, Preston T, Vermeulen K, De Preter V, Hamer HM, Van den Mooter G, De Vuyst L, Courtin CM, Annaert P, Delcour JA, Verbeke KA. Systemic availability and metabolism of colonic-derived short-chain fatty acids in healthy subjects: a stable isotope study. *J Physiol* 2017; **595**: 541-555 [PMID: 27510655 DOI: 10.1113/JP272613]

32 **Zhang L**, Yang G, Untereiner A, Ju Y, Wu L, Wang R. Hydrogen sulfide impairs glucose utilization and increases gluconeogenesis in hepatocytes. *Endocrinology* 2013; **154**: 114-126 [PMID: 23183179 DOI: 10.1210/en.2012-1658]

33 **Chen S**, Henderson A, Petriello MC, Romano KA, Gearing M, Miao J, Schell M, Sandoval-Espinola WJ, Tao J, Sha B, Graham M, Crooke R, Kleinridders A, Balskus EP, Rey FE, Morris AJ, Biddinger SB. Trimethylamine N-Oxide Binds and Activates PERK to Promote Metabolic Dysfunction. *Cell Metab* 2019; **30**: 1141-1151.e5 [PMID: 31543404 DOI: 10.1016/j.cmet.2019.08.021]

34 **Dordević D**, Jančíková S, Vítězová M, Kushkevych I. Hydrogen sulfide toxicity in the gut environment: Meta-analysis of sulfate-reducing and lactic acid bacteria in inflammatory processes. *J Adv Res* 2021; **27**: 55-69 [PMID: 33318866 DOI: 10.1016/j.jare.2020.03.003]

35 **Jain SK**, Bull R, Rains JL, Bass PF, Levine SN, Reddy S, McVie R, Bocchini JA. Low levels of hydrogen sulfide in the blood of diabetes patients and streptozotocin-treated rats causes vascular inflammation? *Antioxid Redox Signal* 2010; **12**: 1333-1337 [PMID: 20092409 DOI: 10.1089/ars.2009.2956]

36 **Suzuki K**, Sagara M, Aoki C, Tanaka S, Aso Y. Clinical Implication of Plasma Hydrogen Sulfide Levels in Japanese Patients with Type 2 Diabetes. *Intern Med* 2017; **56**: 17-21 [PMID: 28049995 DOI: 10.2169/internalmedicine.56.7403]

37 **Rath S**, Rud T, Pieper DH, Vital M. Potential TMA-Producing Bacteria Are Ubiquitously Found in Mammalia. *Front Microbiol* 2019; **10**: 2966 [PMID: 31998260 DOI: 10.3389/fmicb.2019.02966]

38 **Tang WH**, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, Wu Y, Hazen SL. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med* 2013; **368**: 1575-1584 [PMID: 23614584 DOI: 10.1056/NEJMoa1109400]

39 **Wang Z**, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, Feldstein AE, Britt EB, Fu X, Chung YM, Wu Y, Schauer P, Smith JD, Allayee H, Tang WH, DiDonato JA, Lusis AJ, Hazen SL. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* 2011; **472**: 57-63 [PMID: 21475195 DOI: 10.1038/nature09922]

40 **Svingen GF**, Schartum-Hansen H, Pedersen ER, Ueland PM, Tell GS, Mellgren G, Njølstad PR, Seifert R, Strand E, Karlsson T, Nygård O. Prospective Associations of Systemic and Urinary Choline Metabolites with Incident Type 2 Diabetes. *Clin Chem* 2016; **62**: 755-765 [PMID: 26980210 DOI: 10.1373/clinchem.2015.250761]

41 **Dambrova M**, Latkovskis G, Kuka J, Strele I, Konrade I, Grinberga S, Hartmane D, Pugovics O, Erglis A, Liepinsh E. Diabetes is Associated with Higher Trimethylamine N-oxide Plasma Levels. *Exp Clin Endocrinol Diabetes* 2016; **124**: 251-256 [PMID: 27123785 DOI: 10.1055/s-0035-1569330]

42 **Miao J**, Ling AV, Manthena PV, Gearing ME, Graham MJ, Crooke RM, Croce KJ, Esquejo RM, Clish CB; Morbid Obesity Study Group, Vicent D, Biddinger SB. Flavin-containing monooxygenase 3 as a potential player in diabetes-associated atherosclerosis. *Nat Commun* 2015; **6**: 6498 [PMID: 25849138 DOI: 10.1038/ncomms7498]

43 **Gao X**, Liu X, Xu J, Xue C, Xue Y, Wang Y. Dietary trimethylamine N-oxide exacerbates impaired glucose tolerance in mice fed a high fat diet. *J Biosci Bioeng* 2014; **118**: 476-481 [PMID: 24721123 DOI: 10.1016/j.jbiosc.2014.03.001]

44 **Brown MS**, Goldstein JL. Selective *vs* total insulin resistance: a pathogenic paradox. *Cell Metab* 2008; **7**: 95-96 [PMID: 18249166 DOI: 10.1016/j.cmet.2007.12.009]

45 **Russell WR**, Duncan SH, Scobbie L, Duncan G, Cantlay L, Calder AG, Anderson SE, Flint HJ. Major phenylpropanoid-derived metabolites in the human gut can arise from microbial fermentation of protein. *Mol Nutr Food Res* 2013; **57**: 523-535 [PMID: 23349065 DOI: 10.1002/mnfr.201200594]

46 **Hoyles L**, Fernández-Real JM, Federici M, Serino M, Abbott J, Charpentier J, Heymes C, Luque JL, Anthony E, Barton RH, Chilloux J, Myridakis A, Martinez-Gili L, Moreno-Navarrete JM, Benhamed F, Azalbert V, Blasco-Baque V, Puig J, Xifra G, Ricart W, Tomlinson C, Woodbridge M, Cardellini M, Davato F, Cardolini I, Porzio O, Gentileschi P, Lopez F, Foufelle F, Butcher SA, Holmes E, Nicholson JK, Postic C, Burcelin R, Dumas ME. Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women. *Nat Med* 2018; **24**: 1070-1080 [PMID: 29942096 DOI: 10.1038/s41591-018-0061-3]

47 **den Besten G**, Bleeker A, Gerding A, van Eunen K, Havinga R, van Dijk TH, Oosterveer MH, Jonker JW, Groen AK, Reijngoud DJ, Bakker BM. Short-Chain Fatty Acids Protect Against High-Fat Diet-Induced Obesity *via* a PPARγ-Dependent Switch From Lipogenesis to Fat Oxidation. *Diabetes* 2015; **64**: 2398-2408 [PMID: 25695945 DOI: 10.2337/db14-1213]

48 **Gao Z**, Yin J, Zhang J, Ward RE, Martin RJ, Lefevre M, Cefalu WT, Ye J. Butyrate improves insulin sensitivity and increases energy expenditure in mice. *Diabetes* 2009; **58**: 1509-1517 [PMID: 19366864 DOI: 10.2337/db08-1637]

49 **Mollica MP**, Mattace Raso G, Cavaliere G, Trinchese G, De Filippo C, Aceto S, Prisco M, Pirozzi C, Di Guida F, Lama A, Crispino M, Tronino D, Di Vaio P, Berni Canani R, Calignano A, Meli R. Butyrate Regulates Liver Mitochondrial Function, Efficiency, and Dynamics in Insulin-Resistant Obese Mice. *Diabetes* 2017; **66**: 1405-1418 [PMID: 28223285 DOI: 10.2337/db16-0924]

50 **Sato S**, Jung H, Nakagawa T, Pawlosky R, Takeshima T, Lee WR, Sakiyama H, Laxman S, Wynn RM, Tu BP, MacMillan JB, De Brabander JK, Veech RL, Uyeda K. Metabolite Regulation of Nuclear Localization of Carbohydrate-response Element-binding Protein (ChREBP): ROLE OF AMP AS AN ALLOSTERIC INHIBITOR. *J Biol Chem* 2016; **291**: 10515-10527 [PMID: 26984404 DOI: 10.1074/jbc.M115.708982]

51 **Yamashita H**, Fujisawa K, Ito E, Idei S, Kawaguchi N, Kimoto M, Hiemori M, Tsuji H. Improvement of obesity and glucose tolerance by acetate in Type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. *Biosci Biotechnol Biochem* 2007; **71**: 1236-1243 [PMID: 17485860 DOI: 10.1271/bbb.60668]

52 **Kondo T**, Kishi M, Fushimi T, Kaga T. Acetic acid upregulates the expression of genes for fatty acid oxidation enzymes in liver to suppress body fat accumulation. *J Agric Food Chem* 2009; **57**: 5982-5986 [PMID: 19469536 DOI: 10.1021/jf900470c]

53 **Sahuri-Arisoylu M**, Brody LP, Parkinson JR, Parkes H, Navaratnam N, Miller AD, Thomas EL, Frost G, Bell JD. Reprogramming of hepatic fat accumulation and 'browning' of adipose tissue by the short-chain fatty acid acetate. *Int J Obes (Lond)* 2016; **40**: 955-963 [PMID: 26975441 DOI: 10.1038/ijo.2016.23]

54 **Kahn BB**, Flier JS. Obesity and insulin resistance. *J Clin Invest* 2000; **106**: 473-481 [PMID: 10953022 DOI: 10.1172/jci10842]

55 **Goto T**, Kim YI, Furuzono T, Takahashi N, Yamakuni K, Yang HE, Li Y, Ohue R, Nomura W, Sugawara T, Yu R, Kitamura N, Park SB, Kishino S, Ogawa J, Kawada T. 10-oxo-12(Z)-octadecenoic acid, a linoleic acid metabolite produced by gut lactic acid bacteria, potently activates PPARγ and stimulates adipogenesis. *Biochem Biophys Res Commun* 2015; **459**: 597-603 [PMID: 25749343 DOI: 10.1016/j.bbrc.2015.02.154]

56 **Guilherme A**, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nat Rev Mol Cell Biol* 2008; **9**: 367-377 [PMID: 18401346 DOI: 10.1038/nrm2391]

57 **Perry RJ**, Camporez JG, Kursawe R, Titchenell PM, Zhang D, Perry CJ, Jurczak MJ, Abudukadier A, Han MS, Zhang XM, Ruan HB, Yang X, Caprio S, Kaech SM, Sul HS, Birnbaum MJ, Davis RJ, Cline GW, Petersen KF, Shulman GI. Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. *Cell* 2015; **160**: 745-758 [PMID: 25662011 DOI: 10.1016/j.cell.2015.01.012]

58 **Morigny P**, Houssier M, Mouisel E, Langin D. Adipocyte lipolysis and insulin resistance. *Biochimie* 2016; **125**: 259-266 [PMID: 26542285 DOI: 10.1016/j.biochi.2015.10.024]

59 **Hong YH**, Nishimura Y, Hishikawa D, Tsuzuki H, Miyahara H, Gotoh C, Choi KC, Feng DD, Chen C, Lee HG, Katoh K, Roh SG, Sasaki S. Acetate and propionate short chain fatty acids stimulate adipogenesis *via* GPCR43. *Endocrinology* 2005; **146**: 5092-5099 [PMID: 16123168 DOI: 10.1210/en.2005-0545]

60 **Ge H**, Li X, Weiszmann J, Wang P, Baribault H, Chen JL, Tian H, Li Y. Activation of G protein-coupled receptor 43 in adipocytes leads to inhibition of lipolysis and suppression of plasma free fatty acids. *Endocrinology* 2008; **149**: 4519-4526 [PMID: 18499755 DOI: 10.1210/en.2008-0059]

61 **Jocken JWE**, González Hernández MA, Hoebers NTH, van der Beek CM, Essers YPG, Blaak EE, Canfora EE. Short-Chain Fatty Acids Differentially Affect Intracellular Lipolysis in a Human White Adipocyte Model. *Front Endocrinol (Lausanne)* 2017; **8**: 372 [PMID: 29375478 DOI: 10.3389/fendo.2017.00372]

62 **Scheja L**, Heeren J. The endocrine function of adipose tissues in health and cardiometabolic disease. *Nat Rev Endocrinol* 2019; **15**: 507-524 [PMID: 31296970 DOI: 10.1038/s41574-019-0230-6]

63 **Smith U**, Kahn BB. Adipose tissue regulates insulin sensitivity: role of adipogenesis, de novo lipogenesis and novel lipids. *J Intern Med* 2016; **280**: 465-475 [PMID: 27699898 DOI: 10.1111/joim.12540]

64 **Zatterale F**, Longo M, Naderi J, Raciti GA, Desiderio A, Miele C, Beguinot F. Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. *Front Physiol* 2019; **10**: 1607 [PMID: 32063863 DOI: 10.3389/fphys.2019.01607]

65 **Shoelson SE**, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest* 2006; **116**: 1793-1801 [PMID: 16823477 DOI: 10.1172/jci29069]

66 **Al-Lahham S**, Roelofsen H, Rezaee F, Weening D, Hoek A, Vonk R, Venema K. Propionic acid affects immune status and metabolism in adipose tissue from overweight subjects. *Eur J Clin Invest* 2012; **42**: 357-364 [PMID: 21913915 DOI: 10.1111/j.1365-2362.2011.02590.x]

67 **Ohira H**, Fujioka Y, Katagiri C, Mamoto R, Aoyama-Ishikawa M, Amako K, Izumi Y, Nishiumi S, Yoshida M, Usami M, Ikeda M. Butyrate attenuates inflammation and lipolysis generated by the interaction of adipocytes and macrophages. *J Atheroscler Thromb* 2013; **20**: 425-442 [PMID: 23470566 DOI: 10.5551/jat.15065]

68 **Townsend KL**, Tseng YH. Brown fat fuel utilization and thermogenesis. *Trends Endocrinol Metab* 2014; **25**: 168-177 [PMID: 24389130 DOI: 10.1016/j.tem.2013.12.004]

69 **Lizcano F**. The Beige Adipocyte as a Therapy for Metabolic Diseases. *Int J Mol Sci* 2019; **20** [PMID: 31614705 DOI: 10.3390/ijms20205058]

70 **O'Callaghan A**, van Sinderen D. Bifidobacteria and Their Role as Members of the Human Gut Microbiota. *Front Microbiol* 2016; **7**: 925 [PMID: 27379055 DOI: 10.3389/fmicb.2016.00925]

71 **Shimizu J**, Kubota T, Takada E, Takai K, Fujiwara N, Arimitsu N, Murayama MA, Ueda Y, Wakisaka S, Suzuki T, Suzuki N. Propionate-producing bacteria in the intestine may associate with skewed responses of IL10-producing regulatory T cells in patients with relapsing polychondritis. *PLoS One* 2018; **13**: e0203657 [PMID: 30235279 DOI: 10.1371/journal.pone.0203657]

72 **Lordan C**, Thapa D, Ross RP, Cotter PD. Potential for enriching next-generation health-promoting gut bacteria through prebiotics and other dietary components. *Gut Microbes* 2020; **11**: 1-20 [PMID: 31116628 DOI: 10.1080/19490976.2019.1613124]

73 **Hanatani S**, Motoshima H, Takaki Y, Kawasaki S, Igata M, Matsumura T, Kondo T, Senokuchi T, Ishii N, Kawashima J, Kukidome D, Shimoda S, Nishikawa T, Araki E. Acetate alters expression of genes involved in beige adipogenesis in 3T3-L1 cells and obese KK-Ay mice. *J Clin Biochem Nutr* 2016; **59**: 207-214 [PMID: 27895388 DOI: 10.3164/jcbn.16-23]

74 **Li Z**, Yi CX, Katiraei S, Kooijman S, Zhou E, Chung CK, Gao Y, van den Heuvel JK, Meijer OC, Berbée JFP, Heijink M, Giera M, Willems van Dijk K, Groen AK, Rensen PCN, Wang Y. Butyrate reduces appetite and activates brown adipose tissue *via* the gut-brain neural circuit. *Gut* 2018; **67**: 1269-1279 [PMID: 29101261 DOI: 10.1136/gutjnl-2017-314050]

75 **Yamashita H**, Maruta H, Jozuka M, Kimura R, Iwabuchi H, Yamato M, Saito T, Fujisawa K, Takahashi Y, Kimoto M, Hiemori M, Tsuji H. Effects of acetate on lipid metabolism in muscles and adipose tissues of type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. *Biosci Biotechnol Biochem* 2009; **73**: 570-576 [PMID: 19270372 DOI: 10.1271/bbb.80634]

76 **Bouter K**, Bakker GJ, Levin E, Hartstra AV, Kootte RS, Udayappan SD, Katiraei S, Bahler L, Gilijamse PW, Tremaroli V, Stahlman M, Holleman F, van Riel NAW, Verberne HJ, Romijn JA, Dallinga-Thie GM, Serlie MJ, Ackermans MT, Kemper EM, Willems van Dijk K, Backhed F, Groen AK, Nieuwdorp M. Differential metabolic effects of oral butyrate treatment in lean *vs* metabolic syndrome subjects. *Clin Transl Gastroenterol* 2018; **9**: 155 [PMID: 29799027 DOI: 10.1038/s41424-018-0025-4]

77 **Canfora EE**, van der Beek CM, Jocken JWE, Goossens GH, Holst JJ, Olde Damink SWM, Lenaerts K, Dejong CHC, Blaak EE. Colonic infusions of short-chain fatty acid mixtures promote energy metabolism in overweight/obese men: a randomized crossover trial. *Sci Rep* 2017; **7**: 2360 [PMID: 28539646 DOI: 10.1038/s41598-017-02546-x]

78 **van der Beek CM**, Canfora EE, Lenaerts K, Troost FJ, Damink SWMO, Holst JJ, Masclee AAM, Dejong CHC, Blaak EE. Distal, not proximal, colonic acetate infusions promote fat oxidation and improve metabolic markers in overweight/obese men. *Clin Sci (Lond)* 2016; **130**: 2073-2082 [PMID: 27439969 DOI: 10.1042/CS20160263]

79 **Chambers ES**, Byrne CS, Aspey K, Chen Y, Khan S, Morrison DJ, Frost G. Acute oral sodium propionate supplementation raises resting energy expenditure and lipid oxidation in fasted humans. *Diabetes Obes Metab* 2018; **20**: 1034-1039 [PMID: 29134744 DOI: 10.1111/dom.13159]

80 **Christie S**, Wittert GA, Li H, Page AJ. Involvement of TRPV1 Channels in Energy Homeostasis. *Front Endocrinol (Lausanne)* 2018; **9**: 420 [PMID: 30108548 DOI: 10.3389/fendo.2018.00420]

81 **Kim M**, Furuzono T, Yamakuni K, Li Y, Kim YI, Takahashi H, Ohue-Kitano R, Jheng HF, Takahashi N, Kano Y, Yu R, Kishino S, Ogawa J, Uchida K, Yamazaki J, Tominaga M, Kawada T, Goto T. 10-oxo-12(*Z*)-octadecenoic acid, a linoleic acid metabolite produced by gut lactic acid bacteria, enhances energy metabolism by activation of TRPV1. *FASEB J* 2017; **31**: 5036-5048 [PMID: 28754711 DOI: 10.1096/fj.201700151R]

82 **Takahashi Y**, Kushiro M, Shinohara K, Ide T. Dietary conjugated linoleic acid reduces body fat mass and affects gene expression of proteins regulating energy metabolism in mice. *Comp Biochem Physiol B Biochem Mol Biol* 2002; **133**: 395-404 [PMID: 12431407 DOI: 10.1016/s1096-4959(02)00164-1]

83 **Park Y**, Park Y. Conjugated fatty acids increase energy expenditure in part by increasing voluntary movement in mice. *Food Chem* 2012; **133**: 400-409 [PMID: 25683412 DOI: 10.1016/j.foodchem.2012.01.051]

84 **Lee HY**, Park JH, Seok SH, Baek MW, Kim DJ, Lee KE, Paek KS, Lee Y, Park JH. Human originated bacteria, Lactobacillus rhamnosus PL60, produce conjugated linoleic acid and show anti-obesity effects in diet-induced obese mice. *Biochim Biophys Acta* 2006; **1761**: 736-744 [PMID: 16807088 DOI: 10.1016/j.bbalip.2006.05.007]

85 **Koepsell H**. Glucose transporters in the small intestine in health and disease. *Pflugers Arch* 2020; **472**: 1207-1248 [PMID: 32829466 DOI: 10.1007/s00424-020-02439-5]

86 **Pavlic M**, Xiao C, Szeto L, Patterson BW, Lewis GF. Insulin acutely inhibits intestinal lipoprotein secretion in humans in part by suppressing plasma free fatty acids. *Diabetes* 2010; **59**: 580-587 [PMID: 20028946 DOI: 10.2337/db09-1297]

87 **Ussar S**, Haering MF, Fujisaka S, Lutter D, Lee KY, Li N, Gerber GK, Bry L, Kahn CR. Regulation of Glucose Uptake and Enteroendocrine Function by the Intestinal Epithelial Insulin Receptor. *Diabetes* 2017; **66**: 886-896 [PMID: 28096258 DOI: 10.2337/db15-1349]

88 **Federico LM**, Naples M, Taylor D, Adeli K. Intestinal insulin resistance and aberrant production of apolipoprotein B48 Lipoproteins in an animal model of insulin resistance and metabolic dyslipidemia: evidence for activation of protein tyrosine phosphatase-1B, extracellular signal-related kinase, and sterol regulatory element-binding protein-1c in the fructose-fed hamster intestine. *Diabetes* 2006; **55**: 1316-1326 [PMID: 16644688 DOI: 10.2337/db04-1084]

89 **Croset M**, Rajas F, Zitoun C, Hurot JM, Montano S, Mithieux G. Rat small intestine is an insulin-sensitive gluconeogenic organ. *Diabetes* 2001; **50**: 740-746 [PMID: 11289037 DOI: 10.2337/diabetes.50.4.740]

90 **Rajas F**, Croset M, Zitoun C, Montano S, Mithieux G. Induction of PEPCK gene expression in insulinopenia in rat small intestine. *Diabetes* 2000; **49**: 1165-1168 [PMID: 10909974 DOI: 10.2337/diabetes.49.7.1165]

91 **De Vadder F**, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchampt A, Bäckhed F, Mithieux G. Microbiota-generated metabolites promote metabolic benefits *via* gut-brain neural circuits. *Cell* 2014; **156**: 84-96 [PMID: 24412651 DOI: 10.1016/j.cell.2013.12.016]

92 **De Vadder F**, Kovatcheva-Datchary P, Zitoun C, Duchampt A, Bäckhed F, Mithieux G. Microbiota-Produced Succinate Improves Glucose Homeostasis *via* Intestinal Gluconeogenesis. *Cell Metab* 2016; **24**: 151-157 [PMID: 27411015 DOI: 10.1016/j.cmet.2016.06.013]

93 **Troy S**, Soty M, Ribeiro L, Laval L, Migrenne S, Fioramonti X, Pillot B, Fauveau V, Aubert R, Viollet B, Foretz M, Leclerc J, Duchampt A, Zitoun C, Thorens B, Magnan C, Mithieux G, Andreelli F. Intestinal gluconeogenesis is a key factor for early metabolic changes after gastric bypass but not after gastric lap-band in mice. *Cell Metab* 2008; **8**: 201-211 [PMID: 18762021 DOI: 10.1016/j.cmet.2008.08.008]

94 **Duraffourd C**, De Vadder F, Goncalves D, Delaere F, Penhoat A, Brusset B, Rajas F, Chassard D, Duchampt A, Stefanutti A, Gautier-Stein A, Mithieux G. Mu-opioid receptors and dietary protein stimulate a gut-brain neural circuitry limiting food intake. *Cell* 2012; **150**: 377-388 [PMID: 22771138 DOI: 10.1016/j.cell.2012.05.039]

95 **De Vadder F**, Plessier F, Gautier-Stein A, Mithieux G. Vasoactive intestinal peptide is a local mediator in a gut-brain neural axis activating intestinal gluconeogenesis. *Neurogastroenterol Motil* 2015; **27**: 443-448 [PMID: 25586379 DOI: 10.1111/nmo.12508]

96 **Mithieux G**, Misery P, Magnan C, Pillot B, Gautier-Stein A, Bernard C, Rajas F, Zitoun C. Portal sensing of intestinal gluconeogenesis is a mechanistic link in the diminution of food intake induced by diet protein. *Cell Metab* 2005; **2**: 321-329 [PMID: 16271532 DOI: 10.1016/j.cmet.2005.09.010]

97 **Soty M**, Gautier-Stein A, Rajas F, Mithieux G. Gut-Brain Glucose Signaling in Energy Homeostasis. *Cell Metab* 2017; **25**: 1231-1242 [PMID: 28591631 DOI: 10.1016/j.cmet.2017.04.032]

98 **Yan Y**, Zhou Z, Kong F, Feng S, Li X, Sha Y, Zhang G, Liu H, Zhang H, Wang S, Hu C, Zhang X. Roux-en-Y Gastric Bypass Surgery Suppresses Hepatic Gluconeogenesis and Increases Intestinal Gluconeogenesis in a T2DM Rat Model. *Obes Surg* 2016; **26**: 2683-2690 [PMID: 27038047 DOI: 10.1007/s11695-016-2157-5]

99 **Zhang X**, Yang S, Chen J, Su Z. Unraveling the Regulation of Hepatic Gluconeogenesis. *Front Endocrinol (Lausanne)* 2018; **9**: 802 [PMID: 30733709 DOI: 10.3389/fendo.2018.00802]

100 **Kovatcheva-Datchary P**, Nilsson A, Akrami R, Lee YS, De Vadder F, Arora T, Hallen A, Martens E, Björck I, Bäckhed F. Dietary Fiber-Induced Improvement in Glucose Metabolism Is Associated with Increased Abundance of Prevotella. *Cell Metab* 2015; **22**: 971-982 [PMID: 26552345 DOI: 10.1016/j.cmet.2015.10.001]

**Footnotes**

**Conflict-of-interest statement:** The authors declare no conflicts of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** February 10, 2021

**First decision:** March 8, 2021

**Article in press:** May 20, 2021

**Specialty type:** Endocrinology and metabolism

**Country/Territory of origin:** South Korea

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Cheng JT, Peng XC **S-Editor:** Gao CC **L-Editor: A P-Editor:** Ma YJ

**Figure Legends**



**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. Isovanillic 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-gamma coactivator 1; G6Pase: Glucose 6-phosphatase.

**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 *in vivo* | Yamashita *et al*[75] |
| Liver | Decreased lipogenesis *in vivo* | den Besten *et al*[47] and Yamashita *et al*[51] |
| Increased lipid oxidation *in vivo* | den Besten *et al*[47], Yamashita *et al*[51], Kondo *et al*[52] and Sahuri-Arisoylu *et al*[53] |
| Adipose tissue | Stimulated adipogenesis *in vitro* | Ge *et al*[60] |
| Inhibited lipolysis *in vitro* and *in vivo* | Hong *et al*[59], Ge *et al*[60] and Jocken *et al*[61] |
| Increased browning *in vitro* and *in vivo* | Sahuri-Arisoylu *et al*[53] and Hanatani *et al*[73] |
| Whole body | Increased energy expenditure and fat oxidation *in vivo* and in humans | den Besten *et al*[47], Canfora *et al*[77] and van der Beek *et al*[78] |
| Propionate | Liver | Suppressed gluconeogenesis *in vitro* | Yoshida *et al*[29] |
| Decreased lipogenesis *in vivo* | den Besten *et al*[47] |
| Increased lipid oxidation *in vivo* | den Besten *et al*[47] |
| Adipose tissue | Increased adipogenesis *in vitro* | Ge *et al*[60] |
| inhibit lipolysis *in vitro* and *in vivo* | Hong *et al*[59] and Ge *et al*[60] |
| Improved inflammation in *ex vivo* | Al-Lahham *et al*[66] |
| Intestine | Promoted gluconeogenesis *in vivo* | De Vadder *et al*[91] |
| Whole body | Increased energy expenditure and fat oxidation *in vivo* and in humans | den Besten *et al*[47], Canfora *et al*[77] and Chambers *et al*[79] |
| Butyrate | Skeletal muscle | Increased lipid oxidation *in vitro* and *in vivo* | Gao *et al*[48] |
| Liver | Decreased lipogenesis *in vivo* | den Besten *et al*[47] |
| Increased lipid oxidation *in vivo* | den Besten *et al*[47], Gao *et al*[48] and Mollica *et al*[49] |
| Adipose tissue | decreased lipolysis *in vitro* | Ohira *et al*[67] |
| Improved inflammation *in vitro* | Ohira *et al*[67] |
| Increased thermogenesis *in vivo* | Gao *et al*[48] and Li *et al*[74] |
| Intestine | Promoted gluconeogenesis *in vitro* and *in vivo* | De Vadder *et al*[91] |
| Whole body | Increased energy expenditure and fat oxidation *in vivo* and in humans | den Besten *et al*[47], Gao *et al*[48] and Canfora *et al*[77] |
| Succinate | Intestine | Promoted gluconeogenesis *in vivo* | De Vadder *et al*[92] |
| **Protein** |
| Protein-derived | Hydrogen sulfide | Liver | Increased gluconeogenesis *in vitro* | Zhang *et al*[32] |
|  |  | Decreased glycogen synthesis *in vitro* | Zhang *et al*[32] |
| Indole | Adipose tissue | Increased inflammation *in vivo* | Virtue *et al*[10] |
| Indole-3-carboxylic acid | Adipose tissue | Increased inflammation *in vivo* | Virtue *et al*[10] |
| Phenylacetic acid | Liver | Increased lipogenesis in *ex vivo* and *in vivo* | Hoyles *et al*[46] |
| **Lipid and others** |
| Linoleic acid-derived | 10-oxo-12(Z)-octadecenoic acid | Adipose tissue | Induced adipogenesis *in vitro* | Goto *et al*[55] |
| Increased thermogenesis *in vivo* | Kim *et al*[81] |
|  | Conjugated linoleic acid | Adipose tissue | Increased energy expenditure | Takahashi *et al*[82], Park *et al*[83] and Lee *et al*[84] |
| Ferulic acid-derived | Ferulic acid 4-O-sulfate and Dihydroferulic acid 4-O-sulfate | Skeletal muscle | Increased glucose uptake *in vitro* | Houghton *et al*[19] |
| Resveratrol-derived | *Trans*-resveratrol 4’-O-glucuro-nide and *Trans*-resveratrol 3-O-sulfate | Skeletal muscle | Increased glucose uptake *in vitro* | Houghton *et al*[19] |
| Berries-derived | Isovanillic acid 3-O-sulfate | Skeletal muscle | Increased glucose uptake *in vitro* | Houghton *et al*[19] |
| Catecin-derived | 4-hydroxy-5-(3,4,5-trihydroxyphenyl) valeric acid, 5-(3,4,5-trihydroxyphenyl)-γ-valerolac-tone, and 5-(3-hydroxyphenyl) valeric acid | Skeletal muscle | Increased glucose uptake *in vitro* | Takagaki *et al*[22] |
| Catecin-derived | 5-(3,5-dihydroxyphenyl)-γ-valerolactone | Skeletal muscle | Increased glucose uptake *in vitro* and *in vivo* | Takagaki *et al*[22] |
| Bacteria-derived | Extracellular vesicles | Skeletal muscle | Decreased glucose uptake *in vivo* | Choi *et al*[20] |
| Choline-derived | Trimethylamine N-oxide | Liver | Increased gluconeogenesis in *ex vivo* and *in vivo* | Chen *et al*[33] and Gao *et al*[43] |
| Adipose tissue | Promoted inflammation *in vivo* | Gao *et al*[43] |



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**