



Review

Sphingosine 1-Phosphate Regulates Obesity and Glucose Homeostasis

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Abstract: One of the major global health and welfare issues is the treatment of obesity and associated metabolic disorders, such as type 2 diabetes mellitus and nonalcoholic fatty liver disease. Obesity, caused by the excessive accumulation of triglycerides in adipose tissues, induces adipocyte dysfunction, followed by inflammation, in adipose tissues and lipotoxicity in nonadipose tissues. Several studies have shown that obesity and glucose homeostasis are influenced by sphingolipid mediators, including ceramide and sphingosine 1-phosphate (S1P). Cellular accumulation of ceramide impairs pancreatic β -cell survival, confers insulin resistance in the liver and the skeletal muscle, and deteriorates adipose tissue inflammation via unknown molecular mechanisms. The roles of S1P are more complicated, because there are five cell-surface S1P receptors (S1PRs: S1P_{1–5}) which have altered functions, different cellular expression patterns, and inapparent intracellular targets. Recent findings, including those by our group, support the notable concept that the pharmacological activation of S1P₁ or S1P₃ improves obesity and associated metabolic disorders, whereas that of S1P₂ has the opposite effect. In addition, the regulation of S1P production by sphingosine kinase (SphK) is an essential factor affecting glucose homeostasis. This review summarizes the current knowledge on SphK/S1P/S1PR signaling in and against obesity, insulin resistance, and associated disorders.

Keywords: adipocyte; adipogenesis; ceramide; glucose tolerance; inflammation; insulin resistance; lipotoxicity; S1P receptor; sphingosine kinase; sphingosine 1-phosphate



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1. Introduction

Obesity is one of the most common medical and welfare problems worldwide. According to the World Health Organization (WHO), >1.9 billion adults worldwide were overweight (body mass index [BMI]: ≥ 25) in 2016, including 650 million who were obese (BMI: ≥ 30), with the prevalence of obesity tripling between 1975 and 2016. Obesity is associated with metabolic syndrome, type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, hepatic steatosis, nonalcoholic fatty liver disease (NAFLD), chronic kidney disease, and a few forms of cancer. Many metabolic diseases are associated with insulin resistance. Lifestyle improvement is important for treating obesity, and considerable efforts have been made to highlight the importance of diet and exercise. However, transforming all patients into healthier conditions is difficult, especially in modern societies with the prevalent overnutrition and lack of exercise that now occurs in developed and developing countries. Therefore, there is a compelling need for alternative strategies to treat obesity, such as easy-to-administer oral therapeutics. Among the numerous candidates, a few researchers have focused on sphingolipid-derived mediators such as sphingosine 1-phosphate (S1P) and ceramide, which have potent and diverse physiological properties.

In this review, we summarize the biological roles of S1P/ceramide in obesity and insulin signaling and discuss the prospects of S1P receptor (S1PR) agonists for use as therapeutics, partly based on our results [1,2], where obesity and T2DM could be treated by modulating specific S1PR signaling. Additionally, there is accumulating evidence showing the roles of S1P/S1PR in the onset and progression of NAFLD and hepatic fibrosis [3–5]. However, this has not been discussed herein because of the current lack of clear relevance to human pathology compared to obesity. We have also deferred a discussion on the roles of S1P/S1PR in cardiovascular, kidney, and inflammatory diseases that has been described in excellent reviews [6–8].

2. Adipocyte and Obesity

2.1. Adipocyte Proliferation and Differentiation

Obesity develops when excess energy is stored in adipocytes as triglycerides (neutral fats). Adipocytes are derived from mesenchymal stem cells and specialize in triglyceride storage. Their cell bodies appear to be occupied by lipid droplets. As the largest endocrine organ in the body, the adipose tissue secretes hormones that regulate glucose, lipid metabolism, and cytokines that regulate systemic inflammation.

Excessive nutrition can increase the size (hypertrophy) and number (hyperplasia) of adipocytes in the adipose tissue. Much evidence supports the idea that adipocyte hypertrophy leads to the onset of insulin resistance and metabolic disorders [9,10]. Adipocytes are classified based on their anatomical location, with the most representative examples being visceral adipocytes, including epididymal, intestinal, and perirenal adipocytes, and subcutaneous adipocytes, such as inguinal adipocytes, although adipocytes exist in the skin, skeletal muscle, pericardium, breast, and bone marrow. Obese visceral adipose tissue (VAT) is considered harmful, whereas obese subcutaneous adipose tissue (SAT) is not [11]. Even when body weight increases similarly, metabolic disorders largely differ depending on whether this increase is associated with adipocyte hypertrophy or hyperplasia or is mainly caused by obesity in the VAT or SAT. The process of how they are determined is mostly unknown; however, understanding “adipogenesis” provides certain clues.

Adipogenesis comprises two phases: determination and terminal differentiation. In the determination phase, mesenchymal stem cells enter the adipocyte lineage through a stimulus called “adipogenic commitment” to form preadipocytes [12]. Although much about this process remains unknown, the route to preadipocytes has been examined by cell lineage tracing. Delta-like homolog 1 (DLK1), a non-canonical Notch ligand, was the first identified marker for preadipocytes [13]. After that, several cell surface preadipocyte markers were identified. Two cell populations, CD24⁺ (Lin⁻, CD34⁺, CD29⁺, Sca-1⁺, and CD24⁺) and CD24⁻ (Lin⁻, CD34⁺, CD29⁺, Sca-1⁺, and CD24⁻), were selected from platelet-derived growth factor receptor α (PDGFR α)-positive stromal vascular cells (SVC) in white adipose tissue [14,15]; however, these markers have been detected in both stem cells and hematopoietic cells, and more specific markers are anticipated. For these situations, we proposed “proliferin” as a novel marker of small proliferative adipocytes, namely, possible beige cell progenitors (preadipocytes) [16]. In the second terminal differentiation phase, fibroblast-like preadipocytes transform into round, lipid-laden cells by expressing several adipocyte-specific genes [17].

Visceral and subcutaneous adipocytes were initially believed to be identical and to differ only in their anatomical locations and systemic effects [18]. However, the Wilms tumor gene, WT1, is specifically expressed in visceral preadipocytes [19]. A study using AdipoChaser mice fed high-fat diets (HFDs) revealed that epididymal adipocytes initiated adipogenesis by 4 weeks. In contrast, subcutaneous adipocytes underwent hypertrophy only after 12 weeks [20]. In addition, visceral adipocytes emerged postnatally, whereas subcutaneous adipocytes developed mainly between embryonic days 14 and 18 [21]. Thus, visceral adipocytes are substantially different from subcutaneous adipocytes, and single-cell sequencing has recently been used to reveal heterogeneity in adipogenic cells [21,22]. Currently, no ideal preadipocyte marker is common to all adipocytes but not expressed in

other progenitor cells [23], and the determinant(s) of adipocyte hypertrophy or hyperplasia remain uncharacterized. Treatment with thiazolidine converts adipocytes from hypertrophy to hyperplasia [10]. Genetic deletion of the transmembrane BAX inhibitor motif containing 1 (TMBIM1), an inhibitor of adipogenesis, induces visceral adipocyte hyperplasia and improves obesity-related metabolic diseases in HFD-fed mice [24]. The distribution of excess nutrients between the visceral and subcutaneous adipocytes is not well understood. However, it is influenced by sex hormones [25].

2.2. Lipotoxicity

Several mechanisms have been proposed to explain the association between obesity and metabolic disease. Adipose tissues are essential for regulating lipid and glucose homeostasis, and patients with lipoatrophic diabetes, who tend to lack adipose tissues, exhibit severe insulin resistance, hyperglycemia, dyslipidemia, and hepatic steatosis [26]. If adipocytes cannot store highly hydrophobic (and, thus, cytotoxic) triglyceride, excessive fat leaks into the blood as non-esterified fatty acids (NEFA). The NEFA in the circulation overflows into other tissues, such as the liver, skeletal muscle, heart, and pancreas, via adipose tissue expandability/expansion [27], and can confer systemic insulin resistance and organ damage, that is, lipotoxicity (Figure 1) [28,29].

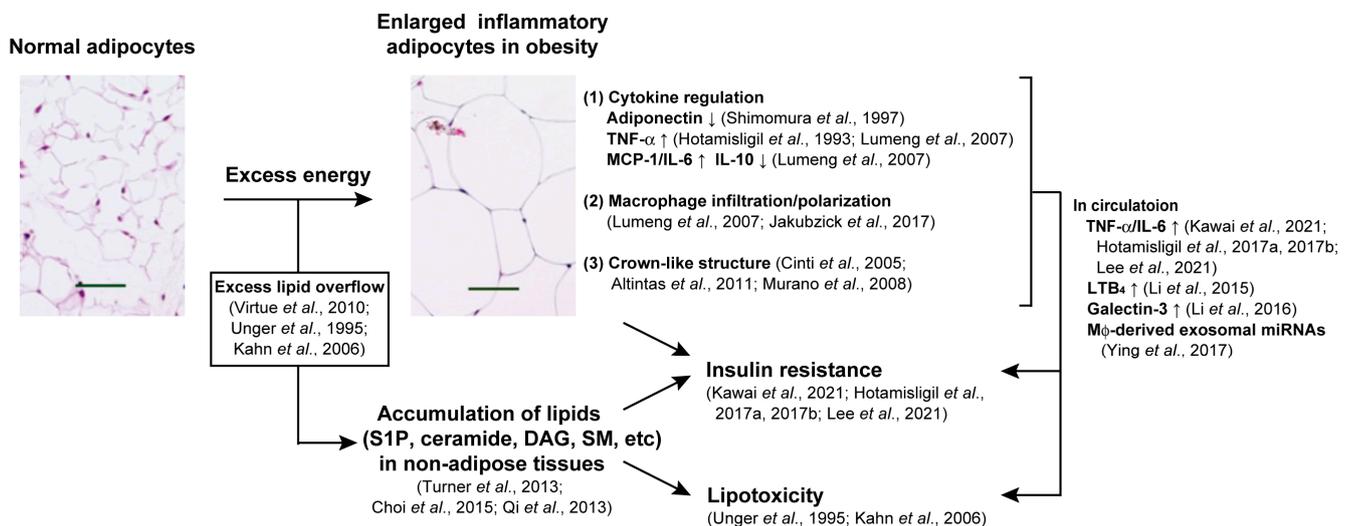


Figure 1. Systemic insulin resistance and lipotoxic damage caused by excessive lipid accumulation in both adipose and nonadipose tissues [27–47].

In experimental animals fed HFDs, the chemical composition of fats and the extent of insulin resistance varied between tissues. Diacylglycerol and short-chain fatty acid-type ceramides accumulate in the liver and skeletal muscle. In contrast, short-type ceramides and sphingomyelin (and diacylglycerol after 16 weeks of HFDs) accumulate in the adipose tissue, which may confer organ-specific insulin resistance [30]. In addition, a lack of adipose tissue causes the loss of “beneficial” hormones, such as leptin and adiponectin. The exacerbation of insulin resistance is partially recovered by supplementation with these hormones in patients with lipoatrophic diabetes [48]. Thus, obesity inhibits the accumulation of triglycerides in adipocytes and decreases adiponectin [31]. Moreover, mitochondrial mass and adipocyte function are suppressed in obese mice [49] and humans [50]. However, whether adipocytes are damaged by mitochondrial dysfunction remains unclear.

2.3. Adipose Tissue Inflammation

Adipose tissue inflammation was first noticed by tumor necrosis factor α (TNF α) expression in the adipose tissue and stromal vascular fraction of obese animals [32]. Cytokines such as interleukin (IL)-6, IL-8, IL-10, and granulocyte colony-stimulating factor

(G-CSF) were reported to be observed in adipocytes [32,33,51]. Monocyte chemoattractant protein-1 (MCP-1) is highly expressed in obese adipose tissue [33] and induces macrophage infiltration into adipose tissue, as well as insulin resistance [52]. These findings imply that MCP-1 secreted by obese adipocytes induces macrophage infiltration into the adipose tissue, which in turn causes adipose tissue inflammation, insulin resistance, and hepatic steatosis (Figure 1). Additionally, most of the adipose tissues from obese mice had classically activated (M1) macrophages that produced various pro-inflammatory cytokines, such as IL-1, IL-6, and TNF α , and reactive oxygen species. In contrast, most of the tissues from lean mice had alternatively activated anti-inflammatory (M2) macrophages [34,35]. A crown-like structure composed of dead or dying hypertrophic adipocytes surrounded by macrophages is a hallmark of chronic inflammation in adipose tissue [36–38]. These findings suggest that obesity induces adipose tissue inflammation and insulin resistance (Figure 1) [39–42].

In obese humans and mice, macrophages accumulate more in VAT than in SAT [37,38,53]. Therefore, inflammation in VAT may be caused by the onset of metabolic disorders [54], although several researchers have observed the importance of inflammation in SAT [55]. Adipose tissue inflammation may induce systemic insulin resistance via the circulating cytokines (e.g., TNF α and IL-6) secreted by M1 macrophages that attenuate insulin signaling in the liver and the skeletal muscle [39–42]. Leukotriene B₄ (LTB₄) and galectin-3 have been postulated as candidates linking adipose tissue inflammation and insulin resistance [43,44]. Furthermore, macrophage-derived exosomal miRNAs impair insulin action in the liver and skeletal muscles [45]. By contrast, obesity can induce M1 macrophage accumulation in the liver, skeletal muscles, and pancreas, which may cause insulin resistance (Figure 1) [42].

The fundamental question is whether obesity-induced adipose tissue inflammation is comparable to the common chronic inflammation associated with infection and cancer. Ordinary chronic inflammation is accompanied by reduced appetite and increased energy expenditure, leading to weight loss and, in the worst cases, cachexia. In contrast, inflammation in obesity does not have this effect [41]. Kratz et al. demonstrated that CD274, CD38, and CD319 were expressed in classically activated M1 macrophages isolated from patients with cystic fibrosis. In contrast, they were hardly observed in metabolically activated M1 macrophages isolated from the adipose tissue of patients with obesity [56]. The expression levels of TNF α and IL-6 were much lower in metabolically activated M1 macrophages than those in classically activated M1 macrophages [56]. Furthermore, obesity-induced lysosomal-dependent lipid metabolism was not observed in classically activated M1 macrophages [57]. Recent studies have revealed that the population of adipose tissue macrophages is more complex than previously expected [58,59]. Thus, although common processes may exist, the inflammation in obese adipose tissues may differ from classical inflammation.

These findings may be related to the failure of multiple anti-inflammatory treatments to ameliorate obesity-induced metabolic disorders. In clinical trials using TNF α -targeted drugs that are effective against rheumatoid arthritis, a few were slightly effective in improving insulin sensitivity [60], while others were not [61,62]. In patients with T2DM, the blockade of IL-1 receptor signaling improves glycemic control and the ability to secrete insulin, but not insulin resistance itself, as evaluated by insulin-regulated gene expression in skeletal muscle and serum adiponectin levels [63]. Although the administration of high doses of salicylate has been shown to improve blood glucose levels in mice [64], no success has been observed in treatments that target adipose tissue inflammation in patients with obese T2DM [39,42].

3. S1P and S1P Receptors

S1P was first described in 1991 as a growth factor derived from membrane sphingolipids [65]. Sphingomyelinase converts sphingomyelin to ceramide, which is metabolized to sphingosine by ceramidase (Figure 2) [66]. Ceramides are synthesized from serine and palmitoyl-CoA through the activities of enzymes such as serine palmitoyltransferase (ser-

ine palmitoyltransferase long-chain base subunit: Sptlc) and ceramide synthase (CerS) (Figure 2) [67]. Obesity causes an excessive flow of saturated fatty acids into adipocytes and other tissues, along with the accumulation of ceramide, a key lipotoxic player [68]. Sphingosine is phosphorylated by sphingosine kinase 1 (SphK1) and SphK2, which have similar catalytic properties but differ in subcellular localization and tissue-specific expression [66]. SphK1 is cytosolic and translocates to the plasma membrane or extracellularly upon activation [67], whereas SphK2 is located in the endoplasmic reticulum, mitochondria, and nucleus [69]. S1P is secreted as a paracrine or endocrine molecule and is an intracellular secondary messenger. Circulating (serum) S1P levels are approximately 500 nM in humans [70], and extracellular S1P binds to high-density lipoproteins via apolipoprotein M (apoM) and albumin (Figure 2) [71]. S1P are degraded by S1P lyase (SPL) or S1P phosphatases (SPP1 and SPP2) [72].

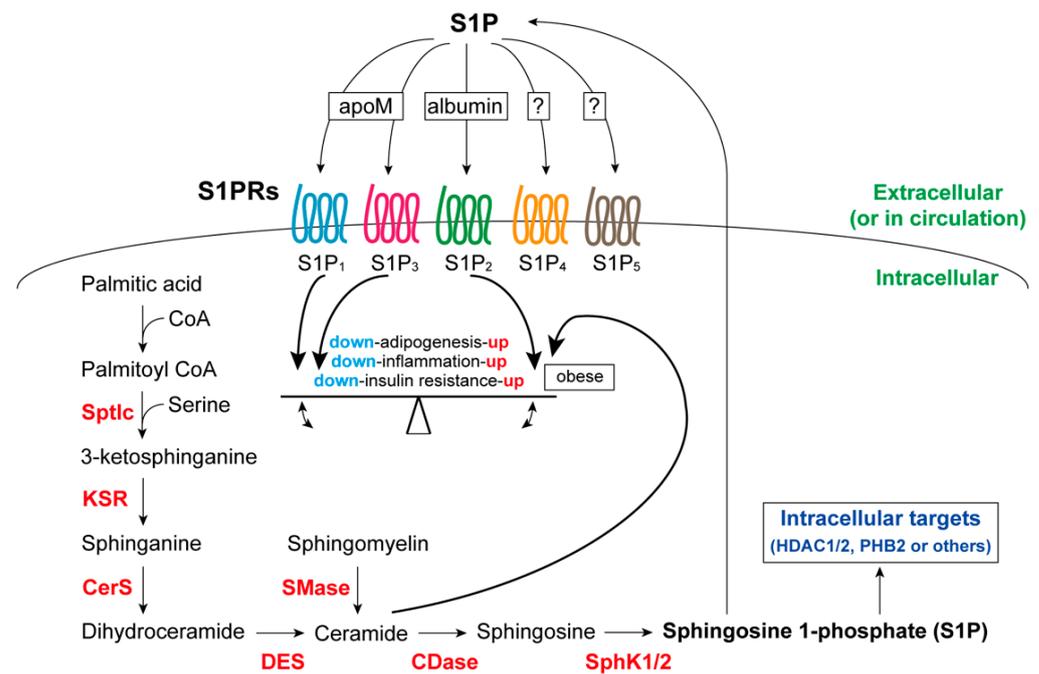


Figure 2. Sphingosine 1-phosphate (S1P) production and associated cell surface receptor signaling that regulates adipose function. Ceramide is produced from sphingomyelin by sphingomyelinase (SMase) or from palmitoyl-CoA and serine via serine palmitoyltransferase (Sptlc), 3-ketosphinganine reductase (KSR), ceramide synthase (CerS), and dihydroceramide desaturase (DES). Ceramide is converted to sphingosine by ceramidase (CDase) and S1P by SphK1/2. S1P acts through intracellular targets (HDAC1/2, PHB2, etc.) or is secreted extracellularly (e.g., in circulation) to affect cell surface S1P receptors (S1P₁–S1P₅). S1P_{1/3} agonists and S1P₂ agonists/ceramide have opposing actions in terms of adipose function: the former prevents obesity and associated adipogenesis, adipocyte inflammation, and insulin resistance, whereas the latter rather promotes such conditions [1,2].

S1P participates in various cellular signaling pathways, including those involved in cell survival, proliferation, migration, and differentiation in multiple organs, through five cognate S1PRs: S1P₁–S1P₅ (Figure 2) [72,73]. S1P₁–S1P₃ are expressed in various cell types, whereas S1P₄ and S1P₅ are expressed exclusively in lymphocytes and dendritic cells, respectively [74]. The characteristics and roles of S1PRs have been described in many reviews [72,73]. Therefore, we only cover the following three issues: First, the role of S1P₂ in inflammation, especially in macrophage function, is complex, and S1P₂ has been proposed to suppress [75] or promote [76] macrophage activity. Similarly, the opposite relationship was observed between S1P₃ and inflammation [77,78], probably attributable to differences in inflammation and the surrounding environment. Second, these receptors may act cooperatively and antagonistically [79,80], underscoring the diverse

physiological actions of S1P. Therefore, when we discuss S1P actions, identification of the S1P receptor subtypes involved becomes indispensable. Third, extracellularly released S1P often acts against intracellular S1P levels. Activation of SphK1 in response to pro-inflammatory stimuli may induce M1 macrophage formation when S1P₁ activation triggers anti-inflammatory responses [81]. The intracellular S1P targets (especially those important in glucose homeostasis) remain to be clarified (Figure 2). However, S1P may directly bind to and inhibit histone deacetylase 1/2 (HDAC1/2) [82] or bind to prohibitin 2 (PHB2) to regulate cytochrome *c* oxidase assembly and mitochondrial respiration [83].

Clinical applications focusing on the potent action of S1P began in the 2010s. FTY720 (FingolimodTM) was the first clinically approved S1P signal modulator for treating multiple sclerosis [84]. FTY720 binds to and activates all S1PRs, except S1P₂, but specifically downregulates S1P₁ in lymphocytes [74,85]. Furthermore, FTY720 suppresses CerS activity but activates ceramide synthesis in cultured cells under certain circumstances [86]. Next-generation S1PR modulators with fewer adverse effects and receptor specificities, including mocravimod (S1P_{1/4/5} agonist), ozanimod (S1P_{1/5} agonist), etrasimod (S1P_{1/4/5} agonist), amiselimod (S1P₁ agonist), ponesimod (S1P_{1/4/5} agonist), siponimod (S1P_{1/5} agonist), and ceralifimod (S1P_{1/5} agonist), were developed and investigated for clinical application in diseases other than multiple sclerosis, including inflammatory bowel disease, psoriasis, atopic dermatitis, rheumatoid arthritis, systemic lupus erythematosus, and certain cancers [87]. In the laboratory, SEW-2871 has been used as a S1P₁ agonist, VPC-23019 as a S1P_{1/3} antagonist, JTE-013 as a S1P₂ antagonist, and CYM-50358 as a S1P₄ antagonist [1,2].

Several drugs that regulate S1P signaling have been developed in addition to S1PR agonists/modulators. Several SphK inhibitors have been developed, including isoform-specific ones [88]. SPL inhibitors LX2931 and LX2932 have also been developed to treat rheumatoid arthritis [89].

4. Tissue-Specific Roles of S1P/S1PR in Insulin Resistance

Obesity-induced insulin resistance occurs in pancreatic β -cells and peripheral tissues such as the liver, adipose tissue, and skeletal muscle [90]. Genetic deletion of insulin receptors in murine adipose tissue, skeletal muscle, or both induces insulin resistance, but not diabetes [91,92], which contrasts with the liver-specific deletion of insulin receptors that causes severe insulin resistance and hyperglycemia [93]. Therefore, hepatic insulin resistance is considered more important in whole-body glucose metabolism. However, the roles of adipose tissues, especially in obese states, dominate. The levels of S1P/ceramide (diacylglycerol/sphingomyelin) and the activation status of SphK/S1PR have been investigated in the tissues and plasma of HFD-fed obese mice (Table 1). S1P and ceramide levels increased in the liver, adipose tissue, skeletal muscle, pancreas, and plasma [30,46], except for ceramide in the pancreas [47]. SphK1 and SphK2 can be activated in the liver [94,95], whereas only SphK1 is activated in adipose tissue [96] and skeletal muscle [94]. Information regarding the S1PR subtypes involved in obesity is limited; however, S1P₃ is upregulated in the liver and adipose tissue [97]. Furthermore, S1P₁ is upregulated, whereas S1P₃ is downregulated in the skeletal muscle [98].

Table 1. Lipid levels and SphK/S1PR activation status in tissues of HFD-fed obese mice.

	Liver	Adipose Tissue	Skeletal Muscle	Pancreas	Plasma
S1P levels	↑ [46]	↑ [46]	↑ [46]	↑ [47]	↑ [46]
Ceramide levels	↑ [30,46]	↑ [30,46]	↑ [30,46]	→ [47]	↑ [46]
Diacylglycerol levels	↑ [30]	↑ [30]	↑ [30]	NE	NE
Sphingomyelin levels	↑ [30]	NE	NE	NE	NE
SphK activation	SphK1↑ [94] SphK1→/SphK2↑ [95]	SphK1↑ [96]	SphK1↑ [94]	NE	NE
S1PR activation	S1P ₃ ↑ [97]	S1P ₃ ↑ [97]	S1P ₁ ↑/S1P ₂ →/S1P ₃ ↓ [98]	NE	NE

NE, not examined; ↑, upregulated; ↓, downregulated; →, no change. The reference numbers are in parentheses.

4.1. Liver

The effects of S1P/S1PR signal modification on the livers of experimental mice are summarized in Table 2. As observed in patients with NAFLD, hepatic insulin resistance is usually associated with hepatic steatosis, resulting from excessive incorporation of fatty acids into the liver and upregulation of de novo lipogenesis. Inhibition of insulin receptor kinase by protein kinase C activation induced by diacylglycerol and reduced expression of insulin receptor substrate 2 (IRS2), a signaling molecule downstream of insulin receptor kinase, could cause hepatic insulin resistance [99]. The paradoxical state of elevated hepatic de novo lipogenesis in the presence of insulin resistance is known as “selective hepatic insulin resistance” [100].

Insulin resistance and NAFLD form a vicious cycle by which they exacerbate each other. NAFLD can be accompanied by inflammation and fibrosis (nonalcoholic steatohepatitis, NASH), which may progress irreversibly to cirrhosis and hepatocellular carcinoma. These pathogeneses, which begin with insulin resistance, have been extensively studied, and the involvement of SphK, S1P, and S1PRs has been proposed [94,99,101]. The sources of sphingolipids and ceramides are long-chain saturated fatty acids deposited in the liver; hence, the amount of ceramide is upregulated in the liver during hepatic steatosis [102]. Ceramide can affect insulin-stimulated Akt activation and subsequent glucose uptake in the liver and skeletal muscle [103], which is another cause of insulin resistance. In HFD-fed obese mouse models, reduced C16:0 ceramide by antisense oligonucleotide knockdown of ceramide synthase 6 (CerS6) improved glucose resistance and insulin sensitivity [104]. S1P, a terminal metabolite of ceramide whose content is increased in the livers of patients with NAFLD [105], induces insulin resistance in rat hepatocytes [93]. Injecting the S1P₂ antagonist JTE-013 daily for seven consecutive days lowered blood glucose levels and increased phosphorylated Akt levels in the liver fractions of HFD-fed obese mice [106]. Hepatic glucose intolerance and insulin resistance have been observed in hepatocyte-specific SphK2-knockout (SphK2^{-/-}) mice [107]. Interestingly, the addition of ARN14974 (an inhibitor of acid ceramidase), but not S1P, restored insulin resistance in SphK2-null Huh7 hepatic cell lines, suggesting that insulin resistance in hepatocyte-specific SphK1^{-/-} mice is associated with the accumulation of sphingosine rather than decreased S1P production [107]. In contrast, the adenoviral overexpression of SphK1 in the liver improved glucose tolerance and hepatic steatosis in KK/Ay diabetic mice [108].

Additionally, the reduction in hepatic steatosis and improvement in insulin signals in the livers of HFD-induced obese mice were accompanied by reduced adiposity induced by adipocyte-specific genetic deletion of Sptlc2 and treatment with its potent inhibitor, “myriocin” [97]. Systemic genetic deletion or pharmacological inhibition (with a specific inhibitor “5C”) of SphK1 reduced hepatic steatosis and upregulated Akt activity in the livers of HFD-induced obese mice [96]. Systemic genetic deletion of S1P₃ exacerbated HFD-induced hepatic steatosis [109]. In contrast, oral administration of JTE-013 (an S1P₂ antagonist) and SEW-2871 (an S1P₁ agonist) failed to alleviate hepatic steatosis [2]. In HFD-induced obese mice, the levels of plasma S1P and its carrier, apoM, were upregulated. Deterioration of insulin resistance was observed in apoM^{-/-} mice, and improved insulin resistance was observed in apoM-overexpressing mice [110].

Table 2. Effects of modification of the SphK1/S1P/S1PR axis on insulin actions in the liver.

Intervention	Applied Mice	Glc. Tol.	Ins. Res.	Steatosis	Insulin Action	Ref.
CerS6 ASO knockdown	HFD obese or ob/ob	Improved	Improved	Improved	NE	[104]
JTE-013 (S1P ₂ blocker)	HFD NZ obese	Improved	NE	NE	p-Akt↑;GSK-3b↑; glycogen synthesis↑	[106]

Table 2. Cont.

Intervention	Applied Mice	Glc. Tol.	Ins. Res.	Steatosis	Insulin Action	Ref.
Hepatocyte-specific SphK2 ^{-/-}	HFD SphK2 ^{-/-}	Impaired	Impaired	Impaired	p-Akt↓; hepatic glucose production↑	[107]
Ad-SphK1 overexpression	HFD KK/Ay	Improved	NE	Improved	p-Akt↑; GSK-3b↑	[108]
Adipocyte-specific Sptlc2 ^{-/-}	HFD Sptlc2 ^{-/-}	Improved	Improved	Improved	hepatic glucose production →	[97]
Myriocin (Sptlc2 inhibitor)	HFD obese	Improved	Improved	Improved	NE	[97]
SphK1 ^{-/-}	HFD SphK1 ^{-/-}	Improved	Improved	Improved	p-Akt ↑	[96]
5C (SphK1 inhibitor)	HFD obese	Improved	Improved	NE	p-Akt ↑	[96]
S1P ₃ ^{-/-}	HFD S1P ₃ ^{-/-}	Impaired	Impaired	Impaired	NE	[109]
JTE-013 or SEW-2871	HFD obese	Improved	NE	→	NE	[2]
ApoM ^{-/-}	HFD obese	Impaired	Impaired	NE	p-Akt ↓	[110]
Ad-apoM overexpression	HFD obese	Improved	Improved	NE	p-Akt ↑	[110]

Glc. Tol., glucose tolerance; Ins. Res., insulin resistance; CerS6, ceramide synthase 6; ASO, antisense oligonucleotide; GSK, glycogen synthetase kinase; NE, not examined; Ad, adenoviral; ↑, upregulated; ↓, downregulated; →, no change. The reference numbers are in parentheses.

4.2. Adipose Tissue

Table 3 summarizes the impact of S1P/S1PR signal modification on adipose tissue. SphK1/2 expression and S1P content were upregulated at the terminal differentiation stage of 3T3-L1 adipocytes, and the suppression of SphK1 (but not SphK2) attenuated their differentiation into mature adipocytes [111]. SphK1 mRNA levels were higher in adipose tissues from ob/ob mice than in those from control mice [96]. Administration of S1P to 3T3-L1 adipocytes attenuated their adipogenic differentiation [112], and S1P inhibited adipogenic differentiation and enhanced the osteogenic differentiation of mesenchymal stem cells [113]. These contradictory results suggest that adipocyte differentiation requires specific amounts of S1P, and excessive S1P levels may inhibit differentiation.

Table 3. Effects of modification of the SphK1/S1P/S1PR axis on insulin actions in the adipose tissue.

Intervention	Applied Mice	BW	FW	Glc. Tol.	Ins. Res.	Size	Inflammation	Insulin Action	Ref.
SphK1 ^{-/-}	HFD SphK1 ^{-/-}	→	↑	Improved	Improved	↓	CLS ↓; M1/M2 ↓	glucose uptake↑	[96]
5C (SphK1 inhibitor)	HFD obese	NE	NE	Improved	Improved	NE	M1/M2 ↓	p-Akt↑	[96]
S1P ₂ ^{-/-}	S1P ₂ ^{-/-}	↓	↓	→	→	↓	M1/M2 →	NE	[1]
S1P ₂ ^{-/-}	HFD S1P ₂ ^{-/-}	→	↓	Improved	Improved	↓	CLS ↓; M1/M2 ↓	NE	[1]
JTE-013	ob/ob	↓	↓	Improved	Improved	↓	M1/M2 ↓	NE	[1,2]
SEW-2871 (S1P ₁ agonist)	ob/ob	↓	↓	Improved	NE	↓	M1/M2 ↓	NE	[2]

Table 3. Cont.

Intervention	Applied Mice	BW	FW	Glc. Tol.	Ins. Res.	Size	Inflammation	Insulin Action	Ref.
S1P ₃ ^{-/-}	HFD S1P ₃ ^{-/-}	→	↓	Impaired	Impaired	NE	CLS ↑; M1/M2 ↑	NE	[109]
FTY720	HFD obese	↓	NE	Improved	NE	NE	M1/M2 ↓	NE	[114]
FTY720	HFD obese	↓	↓	NE	NE	↓	NE	p-Akt↑; p-AMPK↑	[115]
Adipocyte-specific Sptlc2 ^{-/-}	HFD Sptlc2 ^{-/-}	↓	↓	Improved	Improved	↓	CLS ↓; M1/M2 ↓	glucose uptake↑	[97]
Myeloid-specific Sptlc2 ^{-/-}	HFD Sptlc2 ^{-/-}	→	→	→	→	→	CLS →	NE	[97]
Myriocin (Sptlc2 inhibitor)	HFD obese	↓	↓	Improved	Improved	↓	CLS ↓; M1/M2 ↓	NE	[97]

BW, body weight; FW, fat weight; Glc. Tol., glucose tolerance; Ins. Res., insulin resistance; NE, not examined; CLS, crown-like structure; M1/M2, M1 macrophage/M2 macrophage polarization; ↑, upregulated; ↓, downregulated; →, no change.

Compared to the corresponding wild-type mice, HFD-fed SphK1^{-/-} mice exhibited increased adipose tissue weight; smaller adipocyte size; increased expression of adipocyte markers; and improved glucose tolerance, insulin sensitivity, and adipose tissue inflammation [96]. Intraperitoneal injection of 5C (an SphK1 inhibitor) improved glucose tolerance, insulin resistance, and adipose tissue inflammation in HFD-fed mice [96]. Our group has demonstrated that the application of S1P and JTE-013 downregulates adipogenesis. In contrast, the application of VPC23019 (an S1P_{1/3} antagonist) upregulates the adipogenic differentiation of 3T3-L1 and F442A adipocytes [1]. These results suggest that S1P₁ signaling suppresses adipogenic differentiation, whereas S1P₂ accelerates it, and S1P₂ dominates the overall functions of S1P. Regarding preadipocyte proliferation, the blockade of S1P₁ signaling by VPC-23019 inhibited the proliferation of 3T3-L1 and F442A preadipocytes; in contrast, the blockade of S1P₂ signaling by JTE-013 accelerated it [1]. These findings are consistent with the idea that S1P₁ signals accelerate preadipocyte proliferation, whereas S1P₂ signals inhibit it, and S1P₁ governs the overall S1P actions. We further investigated the effect of S1P₂ deletion on adipose tissue and glucose metabolism in S1P₂-knockout (S1P₂^{-/-}) mice [116]. S1P₂^{-/-} mice fed a normal diet had lower body weights and smaller epididymal adipocytes than those in wild-type mice, while displaying glucose tolerance and adipocyte marker gene expression similar to wild-type mice [1]. However, after four weeks of HFD feeding, S1P₂^{-/-} mice exhibited much smaller adipocytes with improved glucose intolerance/insulin sensitivity, accompanied by reduced crown-like structures and improved M1/M2 macrophage polarization in adipose tissue sections [1]. Consequently, we speculate that S1P₂ deletion accelerates preadipocyte proliferation and suppresses adipogenic differentiation, which may induce adipocyte hyperplasia and prevent glucose intolerance, insulin resistance, and adipose tissue inflammation. Additionally, oral administration of JTE-013 to ob/ob mice for four weeks reduced body weight and improved glucose tolerance and insulin sensitivity [1].

Administration of JTE-013 or SEW-2871 for 12 weeks reduced body weight gain and adipocyte size in both epididymal and inguinal adipose tissues of ob/ob mice [2], and improved glucose intolerance and inflammation in epididymal adipose tissue (but not hepatic steatosis); however, all SEW-2871 effects were canceled by co-administration with VPC-23019 [2]. Consistent with the results in HFD-fed S1P₂^{-/-} mice [1], preventing adipose tissue inflammation and glucose intolerance using JTE-013 and SEW-2871 was attributed to reducing adipocyte size rather than weight loss. Moreover, S1P₃-knockout (S1P₃^{-/-}) mice [117] exhibited phenotypes opposite to those of S1P₂^{-/-} mice, that is,

impaired glucose intolerance, adipose tissue inflammation, and reduced Adipoq mRNA expression in the adipose tissue [109]. Conversely, the adenoviral overexpression of S1P₂ in 3T3-L1 adipocytes inhibited adipogenic differentiation [118]. Therefore, the discrepancy in the role(s) of S1P₂ in adipogenic differentiation may be attributed to differences between constitutive S1P₂ deletion in mice [1] and transient exogenous S1P₂ overexpression in cell lines [118]. FTY720 administration in HFD-fed obese mice caused decreased body weight gain, improved glucose tolerance, and adipose tissue inflammation [114], and prevented body weight and fat weight gain [105]. FTY720 reduces adipocyte size, inhibits adipogenesis, and promotes lipolysis via unknown mechanisms [115]. However, if FTY720 acts as an S1P_{1/3/4/5} agonist in adipocytes, these findings may be consistent with our results.

Ceramide accumulation in VAT appeared to correlate with metabolic disorders in mice [97]. In HFD-induced obese mice, adipocyte-specific genetic deletion of Sptlc2 or treatment with its inhibitor myriocin reduced the levels of adipose sphingolipids and improved adipocyte hypertrophy, systemic glucose tolerance, insulin resistance, and adipose tissue inflammation [97]. Myeloid-specific Sptlc2 deletions exhibited reduced Sptlc2 expression and myeloid sphingolipid levels. However, they did not affect body or fat weights, glucose tolerance, insulin sensitivity, or adipose tissue morphology and inflammation; therefore, macrophage sphingolipids do not contribute to the adipose phenotypes that result from global inhibition of Sptlc2 [97].

The regulatory role of S1P in inflammation may be due to either its direct effects on macrophages or its indirect effects on adipocytes; however, previous *in vivo* studies have not fully addressed this question. Several attempts to improve metabolic abnormalities by regulating adipose tissue inflammation have been unsuccessful, and studies employing mice lacking each of the S1PRs in macrophage- or adipocyte-specific manners are anticipated.

4.3. Skeletal Muscle

The effects of S1P/S1PR signal modification in the skeletal muscle, the most abundant tissue, are summarized in Table 4. The roles of sphingolipids in insulin signaling in the skeletal muscle are simpler than those in the liver and adipose tissue; ceramide impairs insulin signals in skeletal muscle, but S1P enhances them [94]. Palmitate induces ceramide generation, thereby preventing insulin-induced Akt activation and glycogen synthesis [119], whereas S1P enhances basal and insulin-induced glucose uptake via S1P₂ in C2C12 myoblasts [120]. Dexamethasone treatment of C2C12 cells induces atrophy accompanied by reduced SphK1 phosphorylation (activation) and reduced intracellular S1P production while maintaining extracellular S1P production and upregulating cell-surface S1P₂ expression, suggesting pathophysiological roles of S1P/S1PR in skeletal muscle [121]. Global transgenic overexpression of SphK1 using the universal CAG promoter in HFD-fed mice improved insulin resistance in the whole body and skeletal muscle, which was associated with decreased intramuscular ceramide accumulation (but not S1P accumulation) compared to that in their respective wild-type littermates [122]. FTY720 administration to HFD-fed mice prevented ceramide accumulation in the skeletal muscle and insulin resistance in the whole body or skeletal muscle without downregulating any S1PR [98]; therefore, the involvement of S1P/S1PR remains unknown. Skeletal muscle secretes IL-6, which can improve glucose tolerance via several mechanisms [123]. Excessive exogenous palmitate induces SphK1 and IL-6 mRNA expression via S1P₃ in mouse myotubes, but not in adipocytes [124]. In addition, adipocyte-specific deletion of Sptlc2, systemic deletion of SphK1, and treatment with 5C improved glucose tolerance and insulin sensitivity in the skeletal muscle [96,97]. Akt phosphorylation levels in the skeletal muscle were attenuated in apoM^{-/-} mice compared to those in wild-type mice, suggesting the involvement of skeletal muscle in systemic glucose intolerance [110]. Compared to the liver and adipose tissue, our knowledge regarding the roles of the SphK/S1P/S1PR axis in the skeletal muscle (and pancreatic β -cells) is rather limited.

Table 4. Effects of modification of the SphK1/S1P/S1PR axis on insulin actions in the skeletal muscle.

Intervention	Applied mice	Glc. Tol.	Ins. Res.	Insulin Action	Ref.
SphK1 overexpression	HFD SphK1 TG	Improved	Improved	Glucose uptake↑	[122]
FTY720	HFD obese	Improved	NE	Glucose uptake↑; p-Akt↑	[98]
Adipocyte-specific Sptlc2 ^{-/-}	HFD Sptlc2 ^{-/-}	Improved	Improved	p-Akt↑	[97]
SphK1 ^{-/-}	HFD SphK1 ^{-/-}	Improved	Improved	p-Akt→	[96]
5C (SphK1 inhibitor)	HFD obese	Improved	Improved	p-Akt→	[96]
ApoM ^{-/-}	HFD obese	Impaired	Impaired	p-Akt↓	[110]

Glc. Tol., glucose tolerance; Ins. Res., insulin resistance; TG, transgenic; NE, not examined; ↑, upregulated; ↓, downregulated; →, no change.

4.4. Pancreatic β -Cells

The effects of S1P/S1PR signal modification on β -cells are summarized in Table 5. Obesity-induced insulin resistance forces pancreatic β -cells to secrete more insulin, which is highly stressful to β -cells, and obesity-induced lipotoxicity causes β -cell failure [90]. Although secreted insulin can exert a negative feedback effect on β -cells through insulin receptors and/or insulin-like growth factor-1 receptors [125], a deficiency in IRS-2 causes β -cell dysfunction, indicating that the insulin signal is essential for the survival and maintenance of β -cells [126]. The exposure of cultured rat primary islet cells to palmitate caused ceramide accumulation, β -cell apoptosis, and reduced insulin secretion [127]. SphK1 knockdown in rat insulinoma INS-1 832/13 cells reduced insulin synthesis and secretion, whereas SphK1 overexpression restored them [128]. Glucose increases the S1P content by activating SphK2 in mouse insulinoma MIN6 cells and mouse pancreatic islet cells, whereas SphK2 knockdown reduces glucose-stimulated insulin secretion [129]. Furthermore, treating mice with an SphK inhibitor induces glucose intolerance and decreases plasma insulin levels [129].

Table 5. Effects of modification of the SphK1/S1P/S1PR axis on insulin actions in pancreatic β -cells.

Intervention	Applied Mice	BW	Glc. Tol.	Ins. Res.	Ins. Secretion	Survival	Ref.
SphK1 ^{-/-}	HFD SphK1 ^{-/-}	→	Impaired	→	↓	↓	[47]
FTY720	<i>db/db</i>	↑	Improved	→	↑	↑	[130]
S1P ₂ ^{-/-}	STZ-induced diabetic	NE	NE	NE	↑	↑	[131]

Glc. Tol., glucose tolerance; Ins. Res., insulin resistance; STZ, streptozotocin; NE, not examined; ↑, upregulated; ↓, downregulated; →, no change.

HFD-fed SphK1^{-/-} mice exhibited more evident diabetic conditions, including reduced plasma insulin levels associated with reduced β -cell mass and increased β -cell apoptosis, than the respective wild-type mice [47]. These results imply that S1P increases insulin synthesis and secretion, although the relationship is more complex. Evidence suggests that intracellular S1P impairs β -cell function and survival, while extracellular S1P protects β -cells [101]. Oral administration of FTY720 prevents the development of diabetes by increasing the proliferation of β -cells without affecting insulin sensitivity, which is mediated by S1P_{1/3} receptors [130]. Conversely, streptozotocin-induced apoptosis of β -cells was attenuated in S1P₂^{-/-} mice, implying that S1P₂ signaling interferes with β -cell survival [131].

4.5. S1P in the Circulation

The physiological roles of S1P in circulation are not fully understood. S1P binds stably to apoM, primarily associated with HDL, or binds unstably to albumin. ApoM-bound S1P activates S1P_{1/3} to protect against IgA nephropathy, whereas albumin-bound S1P

activates S1P₂ to exert deteriorating effects [132]. Therefore, the physiological roles of S1P in circulation may depend on its carrier protein. The APOM polymorphism, rather than serum apoM levels, appears to be correlated with the risk of T2DM [133]. However, serum apoM levels were inversely associated with BMI and the insulin resistance index [110]. ApoM^{-/-} mice exhibited deteriorated insulin resistance, whereas apoM-overexpressing mice showed improvements in insulin resistance, presumably through the activation of S1P_{1/3} signaling [110].

5. Concluding Remarks

Several studies have emphasized the regulatory roles of SphK, S1P, and S1PR signaling in systemic and local insulin sensitivity. Although adipose-tissue-specific deletion of insulin receptors has no effect on systemic glucose metabolism [91], obesity and the accompanying adipose tissue growth are the most important etiologies of insulin resistance. The onset of insulin resistance is linked to several alterations in adipokine secretion, lipotoxicity, and inflammation of adipose tissue (particularly VAT) accompanied by adipocyte hypertrophy (Figure 1). Reduced plasma and adipose tissue S1P levels in SphK1^{-/-} mice improved insulin resistance, which is associated with reducing adipocyte hypertrophy and inflammation in adipose tissue [96]. Our observations that either S1P₁ activation or S1P₂ blockage ameliorated adipocyte hypertrophy, glucose intolerance, and inflammation in the VAT of obese mice [1,2] were consistent with previous results showing that apoM-carrying S1P worked through S1P_{1/3} to improve insulin resistance, whereas albumin-carrying S1P activated S1P₂ to exacerbate it in obese adipocytes (Figure 2) [110,132] and the liver [106]. Hepatic insulin resistance is caused by the accumulation of ceramide and its metabolite, sphingosine [103,104,107]. The upregulation of ceramide interferes with insulin action, whereas S1P improves insulin resistance in C2C12 myoblasts [120]. However, the function of S1P signaling in regulating insulin sensitivity of skeletal muscles *in vivo* has not yet been thoroughly explained. As for pancreatic β -cells, the functions of the SphK/S1P/S1PR axis in insulin secretion and their survival are points of issue. Several studies have supported the idea that either the activation of S1P_{1/3} or the blockade of S1P₂ is beneficial to adipose tissue, liver, and pancreatic β -cells in obese diabetic animals.

Several problems remain before the SphK/S1P/S1PR axis clinical application can begin. Because S1P exerts pleiotropic actions in any type of cell throughout the body, it is conceivable that S1P agonists or antagonists demonstrate unexpected actions beyond the expected actions on target targets. S1P_{1/3} agonists may affect carcinogenesis. In this regard, approved FTY720, which acts on ceramide synthesis and S1P_{1,3,4,5} as either agonist or antagonist depending on cell types is far from ideal, even though they effectively improve metabolic abnormalities induced by obesity in adipose tissue, skeletal muscles, and pancreatic β -cells with rather limited side effects. According to our study, a new class of S1P₁-specific agonists, SEW-2871, and an S1P₂ antagonist, JTE-013, could be used as therapeutic options for obese diabetes patients [1,2]. Because our studies mainly examined the effects of SEW-2871 and JTE-013 on adipocytes, their influences on the liver, skeletal muscle, and pancreatic β -cells should be carefully investigated.

In conclusion, the SphK/S1P/S1PR axis, which drastically regulates adipocyte function and glucose homeostasis, is a potential target for next-generation drugs against obesity and associated metabolic disorders.

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