Role of lipid-derived mediators in skeletal muscle insulin resistance

Annika Taube, Kristin Eckardt, and Juergen Eckel

Institute of Clinical Biochemistry and Pathobiochemistry, German Diabetes Center, Duesseldorf, Germany

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OBESITY HAS BECOME A GROWING THREAT TO GLOBAL HEALTH BY reaching epidemic proportions. It is closely associated with other diseases like hypertension, dyslipidemia, and hyperglycemia. However, most importantly, obesity is a major risk factor for the development of type 2 diabetes mellitus (T2DM). A complication found in >90% of type 2 diabetic patients is an unresponsiveness of skeletal muscle (SkM) cells to the insulin stimulus known as insulin resistance (8). This condition is marked by hyperinsulinemia, enhanced hepatic gluconeogenesis, and impaired insulin-stimulated glucose uptake into SkM cells (88). Furthermore, insulin resistance is considered as an early sign for the development of T2DM (105). Since SkM is a key metabolic tissue, accounting for ~80% of total glucose disposal under insulin-stimulated conditions (17, 65), defects of insulin action in this tissue are central to the pathogenesis of T2DM.

Multiple pathways may lead to the condition of insulin resistance. Well-known and often-described contributors are adipose tissue-derived cytokines. These so-called adipocytokines exert a variety of effects on peripheral tissues, especially on SkM, and are thereby able to impair insulin responsiveness (reviewed in Ref. 96). Furthermore, macrophage infiltration of adipose tissue accompanied by a constant low-grade inflammation has been described. As a consequence of adipocytokines as well as inflammatory mediators such as tumor necrosis factor-α (TNFα), general systemic as well as adipose tissue lipolysis is altered, leading to elevated levels of free fatty acids (FFA). Enhanced availability of liberated as well as dietary FFA has been shown to result in increased amounts of ectopic lipid stores in nonadipose tissues. These lipids together with their metabolites are able to contribute to the development of insulin resistance (see Fig. 1). However, the precise mechanisms by which ectopic lipid stores develop and how they affect insulin signaling are still part of ongoing debate and will be discussed in this review.

Besides FFA, endocannabinoids (ECs) have also been described as another class of lipid-derived mediators that are able to contribute to the pathogenesis of obesity and insulin resistance. The EC system is an important modulator of energy homeostasis and has been shown to be dysregulated in obesity and T2DM (29).

In this review, we will discuss how increased ectopic lipid stores in SkM affect insulin signaling, leading to insulin resistance. Additionally, we will review the concepts of mitochondrial dysfunction and incomplete β-oxidation as possible mechanisms underlying biogenesis of ectopic lipid stores in SkM. Finally, we will summarize the implications of increased levels of lipid-derived endocannabinoids (ECs) for metabolic control in peripheral tissue and the benefits of targeting the EC system.

Ectopic Lipid Stores Impair Organ Function

Obesity, which results from an imbalance between nutritional intake and energy expenditure, is characterized among others by increased amounts of available lipids. Additionally, lipid levels are further elevated by adipose tissue insulin resistance, which is observed frequently in obese patients. Under normal conditions the level of FFA increases during fasting, whereas in the fed state lipolysis in adipose tissue is suppressed by insulin. However, obesity is characterized by an inadequate insulin action in the fed state that resembles conditions of a normal fasted state, resulting in the release of FFA into the circulation. In such states of lipid oversupply, storage of available FFA cannot be accomplished by adipose tissue anymore. Instead, FFA are also stored in other nonadipose...
tissues not intended for long-term lipid storage like SkM, liver, heart, or pancreas (115). As a consequence, increased amounts of ectopic lipid stores are found in obese patients.

Several studies performed in obese individuals have demonstrated a correlation between the amount of ectopic lipid stores found inside SkM cells, referred to as intramyocellular lipids (IMCL), and parameters of lipid oversupply like body mass index (BMI), waist-to-hip ratio, central adiposity, and percent body fat (32, 66, 73, 101). Whereas small amounts of intracellular triglycerides represent an important energy source especially for skeletal and cardiac muscle in periods of low glucose supply, increasing amounts of ectopic lipid depositions have been demonstrated to be able to impair organ function, known as lipotoxicity. Consequently, in the studies mentioned above, an association between the amount of IMCL and impairment of SkM function marked by insulin resistance has been described. This association is further supported by additional studies performed in nonobese, nondiabetic humans (63) as well as in lean offspring of type 2 diabetic patients, a model of in vivo insulin resistance, where the amount of IMCL was identified as a main predictor of muscle, as well as whole body insulin resistance (49, 79). Accordingly, subsequent studies have shown that reduction of IMCL content results in improved insulin sensitivity (75, 91, 98).

Although the majority of studies have reported a correlation between improved insulin sensitivity and reduced IMCL content, some studies have also described improved insulin sensitivity without a reduction of IMCL. Restriction of dietary glycemic index has been shown to improve insulin sensitivity without changes in IMCL content in healthy volunteers (33). Exercise intervention studies in obese Zucker rats (110) and type 2 diabetic patients (15) demonstrated improved SkM insulin sensitivity without corresponding decrease in long-chain acyl-CoA and diacylglycerol (DAG). Furthermore, a study investigating the potential effects of weight loss and physical activity on IMCL content in obese previously sedentary subjects described a significant increase in insulin sensitivity in response to weight loss and exercise without a significant change in IMCL content (41). Instead, they found a significant decrease in lipid droplet size. These authors have proposed that the reduced lipid droplet size may coincide with increased oxidative enzyme capacity, resulting in improved insulin sensitivity. The results of this study suggest that there might not be a straightforward connection between the amount of IMCL and insulin resistance but that other factors, like lipid droplet size, may also play a role.

An additional source for lipid-derived mediators besides IMCL are lipid stores outside SkM in adipocytes interspersed between muscle fibers called extramyocellular lipids (EMCL). Similar to IMCL, a significant association between EMCL content and obesity, percent body fat, and central adiposity has been observed (101). Analysis of EMCL content in obese and/or type 2 diabetic subjects has demonstrated an association between EMCL content and insulin resistance (37). However, no such correlation was found in a study conducted in lean insulin-resistant offspring of type 2 diabetic patients (49, 101). Due to these divergent results, it may be speculated that the influence of EMCL content on insulin sensitivity may not be a direct but rather a secondary effect depending on other parameters of obesity. Further studies are needed to clarify the contributing effects of EMCL to SkM insulin resistance.

Besides SkM, ectopic lipid stores may also develop in other peripheral tissues, where they are able to impair tissue functionality (reviewed in Ref. 107). Accordingly, several studies have described a correlation between obesity and liver steatosis (39, 87) as well as between intrahepatocellular lipids and BMI, percent body fat, and central obesity (109). Increased intrahepatocellular lipid content has been shown to be negatively correlated with whole body and hepatic insulin sensitivity, as demonstrated by impaired suppression of endogenous glucose production and decreased hepatic glycogen synthesis during hyperinsulinemic clamps (3, 62).

Furthermore, correlations have been described between obesity and ectopic lipid stores in cardiac muscle (50, 97, 106). Like in SkM and liver, intramyocardial lipids have adverse effects on organ function. Intramyocardial lipids have been shown to correlate with concentric left ventricular hypertrophy, nonischemic heart failure, and decreased regional systolic performance (97, 106). Furthermore, there is evidence for the development of cardiomyocyte insulin resistance (23).
Lipid-Derived Metabolites Impair SkM Insulin Signaling

The observation that insulin resistance correlates with IMCL content is especially relevant when considering the essential function of SkM as an insulin-responsive organ for whole body glucose homeostasis. However, the complex mechanisms by which IMCL impair insulin signaling are not yet fully unraveled. Although the lipid droplets themselves may not be harmful, they provide a source of substrate to fuel high rates of fatty acid metabolism and to concomitantly generate fatty acid metabolites, which may interfere with insulin signaling. Derivatives like DAG or ceramide are of special interest, and it has been shown that IMCL accumulation is associated with elevated levels of these metabolites (85, 117). They are able to activate PKCoε, -θ, and -ε isozymes as well as IκB kinase (IKKβ) and c-Jun NH2-terminal kinases. These in turn are able to phosphorylate serine/threonine residues of the insulin receptor and of insulin receptor substrate-1 (IRS-1) and decrease phosphorylation of PKB/Akt (90, 100). As a consequence, activation of insulin receptor, IRS-1 (tyrosine phosphorylation), and PKB/Akt are attenuated, impairing insulin signaling and impeding glucose transporter 4 (GLUT4) translocation to the plasma membrane compartment. Hence, insulin-mediated glucose uptake may be reduced or even abrogated. Furthermore, IKKβ is able to activate NF-κB, which in turn regulates the production of proinflammatory cytokines such as TNFα and IL-6 (99).

Recently, an increase of fatty acylcarnitine ester level has been described in muscle and plasma of an obese/insulin-resistant animal model (59, 60). Accumulation of these intermediates may be explained by a lipid-induced upregulation of β-oxidation rates, whereas downstream metabolic pathways such as the tricarboxylic acid (TCA) cycle and the electron transport chain (ETC) are not upregulated accordingly (74), leading to incomplete β-oxidation. Indeed, it has been shown that high-fat feeding decreases levels of organic acid metabolites of the TCA cycle (60). The model of incomplete β-oxidation is further supported by studies that have used either small interfering RNA-mediated silencing of malonyl-CoA decarboxylase (MCD) in human primary myotubes (13) or knockout of MCD in mice (60) to restrict fatty acid uptake into mitochondria. The reduction of MCD causes an increase of malonyl-CoA, which in turn inhibits carnitine palmitoyl transferase I, thereby suppressing fatty acid uptake (70, 84). This manipulation enhances glucose uptake and glucose oxidation in primary human myotubes (13) and protects MCD-/- mice from diet-induced glucose intolerance despite a high level of IMCL (60). Recently, a study in type 2 diabetic African-American women described increased concentrations of fatty acylcarnitines, which were positively correlated with fasting blood Hb A1C (1). Additionally, it was shown that medium-chain acylcarnitines are able to activate NF-κB in a monocyte cell line, thus providing a potential mechanism of how acylcarnitines may interfere with insulin signaling.

Is IMCL Accumulation a Consequence of Mitochondrial Dysfunction?

Although it has been demonstrated that obesity is significantly associated with increased levels of IMCL, the precise mechanism that causes IMCL to accumulate is still a subject of ongoing discussion (44). A concept that has been proposed states that mitochondrial dysfunction results in insufficient oxidation of FFA, leading to accumulation of IMCL. However, studies investigating SkM mitochondrial oxidative capacity in obese and/or insulin-resistant subjects have revealed conflicting results. On the one hand, several studies have described reduced SkM fatty acid oxidation (FAox) in obesity (40, 48, 51, 53, 57) and T2DM (55, 82). On the other hand, studies have reported unchanged FAox rates in obese humans (11, 46) and type 2 diabetic patients (12) or even increased rates in different animal models (24, 45, 114). An explanation for this discrepancy may be found when a closer look at study details is taken. Besides differences in study subjects, like diet-induced vs. genetic obesity or obese insulin-resistant vs. genetically insulin-resistant subjects, divergent methods of analysis also have to be considered. When whole muscle FAox was analyzed, frequently a reduction in FAox capacity was found (40), whereas examination of isolated mitochondria revealed enhanced FAox capacity (24, 45, 114).

When trying to interpret these results, one has to consider that SkM of insulin-resistant obese individuals generally shows some alterations compared with healthy controls. It has been described that SkM of obese individuals exhibits ~30% less mitochondria and a generally higher content of type II muscle fibers, which are characterized by a decreased oxidative capacity. Both features are consequences of sedentary lifestyle, since studies have shown that exercise can normalize muscle mitochondrial content in type 2 diabetic patients (111) and evoke fiber type switching. Furthermore, several studies in obese humans (11) and rats (40, 45) have reported increased amounts of fatty acid transporter CD36 at the plasma membrane of SkM cells accompanied by an enhanced transport of FFA into SkM (11, 42, 113). Additionally, a reduced expression of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), a coactivator that plays a key role in regulating mitochondrial biogenesis, has been described (78). Another observation in SkM of obese individuals is that there is a failure in substrate switching during the transition from fed to fasted state (52, 54, 74).

These alterations might be the reason why FAox in whole muscle was found to be reduced, whereas oxidative capacity of isolated mitochondria was reported to be intact or even increased. In light of these findings, it seems unlikely that mitochondrial dysfunction is the major cause of IMCL accumulation and that, rather, an increased delivery and/or uptake of FFA exceeding SkM energy requirements may underlie its accumulation (44). Nevertheless, it has to be considered that, depending on the subject’s exact physical constitution, other mechanisms may apply. Hence, it has been described that, in aging and severe obesity, pathological changes in mitochondrial structure, morphology, and function can be observed (38, 47, 81), still providing a possible role for mitochondrial dysfunction in the pathogenesis of insulin resistance under these conditions.

Role of PGC-1α and Oxidative Stress

IMCL themselves are unlikely to be deleterious for SkM insulin signaling. Rather, they serve as a source pool for a variety of metabolites, which in turn have detrimental effects on the insulin-signaling cascade. Therefore, the question remains as to why lipids are not completely oxidized to CO2...
Despite reportedly unchanged or increased mitochondrial oxidative capacity. The concept of incomplete β-oxidation provided by Koves et al. (59) and Muoio and Koves (74) might supply an answer. As mentioned above, high rates of mitochondrial β-oxidation may not be accompanied by equivalently enhanced activity of downstream metabolic pathways such as the TCA cycle or the ETC. PGC-1α has been described as an important player in coordinating interaction between these metabolic cycles (59). Therefore, it is interesting to note that several studies have shown a reduced expression of PGC-1α in obesity and T2DM (72, 78) and as a consequence of high-fat feeding (59, 102). Again, exercise deficiency of sedentary individuals may contribute to this situation because it has been described that content of PGC-1α in red muscle fibers (type I) is greater than in white muscle fibers (type II) (59), which, however, are more commonly found in sedentary individuals. Furthermore, studies have shown that exercise is able to increase muscle PGC-1α content. On average, the induced changes of protein expression in rodent muscle ranged from 1.5- to 2.5-fold (10). Since PGC-1α has been shown to 1) stimulate mitochondrial biogenesis, 2) regulate genes involved in oxidative phosphorylation, and 3) coordinate the induction of β-oxidation with downstream metabolic pathways (59), overexpression models to further analyze its role under high-fat conditions have been generated. Surprisingly, muscle-specific overexpression of PGC-1α in transgenic mice has led to augmentation of diet-induced insulin resistance (18). A reason for this unexpected finding may be that massive overexpression of PGC-1α was associated with increased expression of CD36 and acetyl-CoA carboxylase (ACC)2. Consequently, decreased SkM insulin sensitivity may result from increased CD36-mediated FFA uptake, which exceeds FAox capacity. On the other hand, modest overexpression of PGC-1α in muscle leads to increased GLUT4 expression and insulin-stimulated glucose uptake (5), pointing to the importance of balanced changes within physiological limits to allow improvements of insulin sensitivity.

However, if β-oxidation and TCA cycle do not function in a coordinated fashion, rising NADH/NAD and ATP/ADP ratios as well as depletion of free CoA, carnitine, and organic acids may ensue. This high-energy redox state affects TCA cycle and the ETC, resulting in accumulation of acyl-CoAs, acylcarnitines, and finally, the production of reactive oxygen species (ROS) (74). If ROS formation exceeds detoxification mechanisms, oxidative stress may lead to further deleterious effects. TCA cycle enzymes may be inhibited, stress-induced serine kinases may be activated, and fatty acids in the matrix or in the mitochondrial inner membranes might become subject to lipid peroxidation (92). Indeed, it has been shown that lipid peroxides are increased in the obese state and pose a potential risk of further peroxide-induced oxidative damage to mitochondrial matrix, comprised of DNA, RNA, and enzymes. Hence, a protective mechanism limiting the import of FFA in conditions of high FFA availability as well as the production of ROS has been discussed.

Based on the literature available on the regulation of uncoupling proteins (UCP), it has been speculated that SkM UCP3 may play a crucial role in preventing such lipid-induced oxidative damage (19, 92). Indeed, it has been shown that in conditions of high FFA availability, UCP3 activity and expression are upregulated (94). On the other hand, UCP3 is downregulated again when FAox capacity is high, e.g., in endurance training or due to weight loss. It has been speculated that a lack of SkM UCP3 would result in lipid-induced oxidative damage to the mitochondria. Indeed, UCP3-ablated mice are characterized by increased levels of muscular lipid peroxidation and oxidative damage to proteins and DNA (14). Despite an anticipated increase of lipid-induced oxidative stress in type 2 diabetic patients, reduced muscle UCP3 contents have been demonstrated in prediabetic (95) and type 2 diabetic patients (61, 93, 95). This would suggest that, due to impaired availability of protective effects of UCP3, ROS and lipid peroxides may introduce additional oxidative damage, further impairing mitochondrial integrity.

The scenario of general exercise deficiency as a central component of lipid-induced insulin resistance is supported by the endurance-trained paradox. This concept comprises the observation that increased levels of IMCL may be found not only in sedentary individuals but also in endurance-trained athletes. However, in contrast to obese individuals, where an increased level of IMCL content correlates with insulin resistance, endurance-trained athletes remain highly insulin sensitive (86). Explanations for this might be that, besides their increased exercise-induced mitochondrial biogenesis (47), their enhanced content of highly oxidative type I muscle fibers, and their preserved ability of substrate switching, exercise-stimulated expression of PGC-1α (59) also enables complete oxidation of FFA, severely reducing the amounts of deleterious lipid-derived metabolites as well as ROS. Hence, IMCL in SkM of endurance-trained individuals are completely metabolized and serve exclusively as a source for the increased amount of energy required during training. Nevertheless, this model demonstrates that IMCL themselves are not deleterious and that exercise can protect against lipid-induced insulin resistance. The effects of exercise on whole body insulin sensitivity are numerous, and their detailed description would go beyond the scope of this review.

The Peripheral EC System and Its Dysregulation in Obesity

ECs are a family of lipid ligands derived from cell membrane phospholipids that play an important role in the control of energy homeostasis mainly through binding and subsequent activation of type 1 cannabinoid receptors (CB1R). CB1R have been shown to be expressed in central (26, 43, 83, 112) and peripheral tissues like adipose tissue, liver, and SkM (4, 16, 20, 28, 76, 77). The on-demand synthesis of ECs in neurons and their involvement in regulation of neurotransmitter release has been known for some time (83). However, it has been described recently that the components of EC synthesis and degradation are also present in nonneuronal tissues like liver (76) or pancreas (7, 104). Additionally, adipose tissue has also been recognized as a source for EC production, as shown by the expression of the required enzymes for synthesis and degradation as well as by the detection of ECs within the tissue (77, 103). We have recently demonstrated that in vitro-differentiated human adipocytes derived from subcutaneous fat produce and secrete ECs, including anandamide (AEA) and 2-arachidonoyl-ethanolamide (2-AG) (28), thereby confirming the result of an earlier study (36).

In obesity, the EC system becomes dysregulated, as reflected by increased circulating levels of AEA and 2-AG as well as...
elevated levels of 2-AG in visceral adipose tissue (9, 30, 68) of obese patients. Genetically and diet-induced obese animal models show elevated levels of EC in hypothalamus, adipose tissue, liver, and endocrine pancreas (27, 68, 76). The biochemical mechanisms underlying aberrant EC levels are not completely understood, but the increased bioavailability in obesity may be the result of both increased synthesis and decreased degradation (29). Several studies revealed a reduction of mRNA expression and/or activity of the AEA-degrading enzyme fatty acid amide hydrolase (9, 30, 56, 76). Furthermore, downregulation of CB1R expression in visceral and subcutaneous adipose tissue of obese patients compared with lean controls has been described (9, 30, 56). TNFα, which is known to be elevated in obesity, has been identified as one factor directly involved in decreasing mRNA expression of fatty acidamide hydrolase (56). Another study conducted in 3T3-L1 adipocytes revealed a role for insulin in regulating EC levels by rapidly decreasing mRNA expression of synthesizing enzymes as well as by increasing mRNA expression of degrading enzymes upon stimulation (22). However, in insulin-resistant adipocytes, insulin failed to reduce intracellular EC levels. Together, with TNFα-mediated disturbances of EC degradation, absence of insulin effects may contribute to increased concentrations of ECs associated with obesity.

Another aspect that may influence peripheral EC levels could be a certain dietary fatty acid composition, since the availability of biosynthetic precursor may be affected. A study conducted in 3T3-F442A adipocytes showed that incubation of the cells with arachidonic acid (AA) increased the amount of 2-AG and elevated the level of AA esterified in triglycerides or in sn-2 but not in sn-1 position of phospholipids. Treatment with docosahexaenoic acid decreased 2-AG and AEA concentrations as well as the amount of AA esterified in both positions of phospholipids (67). Similar results have been obtained by an earlier study that has analyzed the influence of dietary AA and docosahexaenoic acid on EC concentrations in mouse brain (6, 116). Further feeding studies support the idea that dietary fatty acids are able to influence the levels of ECs (2, 69, 104).

**Effect of Overactivated EC System at Tissue Level**

Several studies have investigated the tissue-specific contribution of ECs to metabolic regulation and the consequences of overactivating vs. antagonizing CB1R. In adipose tissue, EC signaling participates in the differentiation process of adipocytes, and it has been described that chronic activation of CB1R leads to accelerated differentiation (68). Blocking CB1R provides indirect evidence for a potential role in the determination of adipocyte number in adipose tissue since antagonizing the receptor inhibits preadipocyte proliferation (34). In mature adipocytes, stimulation of CB1R causes activation of lipoprotein lipase (20), inhibition of 5′-AMP-activated protein kinase (AMPK) with subsequent inhibition of FAox (58), and enhanced basal as well as insulin-stimulated glucose uptake (35, 77). Under normal conditions these mechanisms are subject to regulation (e.g., by insulin as outlined above), which limits EC levels to avoid excessive lipid accumulation. However, in states of obesity and insulin resistance, this regulation is disturbed. The action of ECs on adipose tissue results in routing excess energy to the adipocytes and enhancing the storage of fat, thereby increasing fat depots. Additionally, stimulation of CB1R has been shown to cause inhibition of adiponectin production and release (68, 80).

In liver, stimulation of CB1R leads to increased de novo fatty acid synthesis as well as increased lipogenesis by inducing expression of lipogenic transcription factor sterol regulatory element-binding protein-1c and its targets ACC1 and fatty acid synthase (76). Similarly to adipose tissue, activation of AMPK is also inhibited in liver. This observation may be implicated in increasing ectopic lipid stores in liver, since AMPK activity has been shown to inhibit lipogenesis and increase lipid oxidation (58). Therefore, elevated levels of ECs associated with obesity contribute to the development of ectopic lipid stores in liver and associated insulin resistance.

However, tissue-specific contribution of the EC system to metabolic regulation in SkM has been investigated less extensively. Very recently, we published a study examining the involvement of ECs in the negative cross-talk between adipose tissue and SkM (28). We used conditioned media generated from in vitro-differentiated human adipocytes to induce insulin resistance in human SkM cells and were able to partially prevent this effect by treating the cells with the selective CB1R antagonist rimonabant. Concerning the very low levels of ECs detected in conditioned media, we assume that ECs play a role in inducing insulin resistance in a complex interplay with other adipocyte-released factors, which may enhance CB1R signaling. Nevertheless, we could demonstrate that stimulation of CB1R in SkM cells with high doses of AEA leads to impaired insulin-stimulated PKB/Akt (Ser473) phosphorylation and reduced insulin-stimulated glucose uptake. Furthermore, we were able to show that activation of extracellular signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase as well as enhanced IRS-1 (Ser307) phosphorylation is involved in mediating the effects of AEA, potentially underlying the development of insulin resistance. The results of our study add ECs to the growing list of adipocyte-derived factors that mediate SkM insulin resistance.

In summary, EC system overactivity leads to enhanced fatty acid synthesis and lipogenesis in adipose and nonadipose tissue and therefore contributes to increased triglyceride storage, hepatic steatosis, and SkM insulin resistance, whereas adiponectin levels are decreased. Numerous studies investigating the effects of blocking CB1R with selective antagonists like rimonabant have collectively demonstrated an overall increase of metabolic parameters like improvement of dyslipidemia, hyperinsulinemia, and insulin sensitivity as well as reduction of inflammation and hepatic steatosis (reviewed in Refs. 25 and 89). These effects are mediated partially by central mechanisms like reduction of food intake. However, it has been shown that food intake-independent effects of CB1R antagonism play an important role as well. Rimonabant has been described to increase expression of adiponectin in adipocytes, which may partially mediate several of the antiobesity effects of rimonabant like reduction of hyperinsulinemia (4) and improvement of insulin sensitivity (71). Additionally, it has been shown that rimonabant is able to J reduce triglyceride levels in plasma and SkM (21), 2 increase glucose uptake in SkM cells (31), and 3 promote mitochondrial biogenesis in adipocytes (108). These data indicate that potential CB1R antagonists, which act exclusively on peripheral systems, should have beneficial effects on treating metabolic dysfunctions associated with obesity and T2DM. Therefore, adverse
effects observed during clinical application of rimonabant, which are caused by affecting the central nervous system, may be circumvented (64).

Concluding Remarks

Due to the central role of SkM insulin resistance in the pathophysiology of T2DM, it has become increasingly more important to understand cellular mechanisms underlying the development of SkM insulin malfunction. In this review we have reported an important role for lipid-derived metabolites such as DAG, ceramide, acylcarnitine, and Ecs in addition to the more classically described adipocytokines. The amount of available conflicting data on the role of IMCL and mitochondrial function indicates the presumed complex nature of the etiology of insulin resistance. Although clear evidence for the contributive role of lipid-derived metabolites exists, many steps of the route leading to SkM insulin resistance have remained unraveled. To be able to combat insulin resistance and therefore also T2DM, further studies investigating possible yet unknown contributing factors and interactions are needed. Understanding these mechanisms might help to find potential new targets for antidiabetic therapy.

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