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The relationship between muscle mitochondrial nutritional overloading and insulin resistance

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The incidence of type 2 diabetes mellitus and insulin resistance is growing rapidly. Multiple organs including the liver, skeletal muscle and adipose tissue control insulin sensitivity coordinately, but the mechanism of skeletal muscle insulin resistance has not yet been fully elucidated. However, there is a growing body of evidence that lipotoxicity induced by mitochondrial dysfunction in skeletal muscle is an important mediator of insulin resistance. However, some recent findings suggest that skeletal mitochondrial dysfunction generated by genetic manipulation is not always correlated with insulin resistance in animal models. A high fat diet can provoke insulin resistance despite a coordinate increase in skeletal muscle mitochondria, which implies that mitochondrial dysfunction is not mandatory in insulin resistance. Furthermore, incomplete fatty acid oxidation by excessive nutrition supply compared to mitochondrial demand can induce insulin resistance without preceding impairment of mitochondrial function. Taken together we suggested that skeletal muscle mitochondrial overloading, not mitochondrial dysfunction, plays a pivotal role in insulin resistance.

Keywords: Insulin resistance; Mitochondria; Lipotoxicity; Fatty acid oxidation; Reactive oxygen species

INTRODUCTION

The incidence of type 2 diabetes mellitus (DM), metabolic syndrome and obesity has been rapidly increasing over the last few decades. The pathogenesis of type 2 DM is mainly characterized by pancreatic beta cell dysfunction and peripheral insulin resistance. Although the mechanism of insulin resistance, which is defined by the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells, has yet to be fully elucidated, recent studies have offered some insight into the role of skeletal muscle insulin resistance in type 2 DM.

Skeletal muscle plays a major role in insulin-mediated glucose uptake, and works as a major reservoir for glucose storage. In the insulin resistant state, impaired insulin-stimulated glucose uptake and reduced glycogen synthesis accounts for more than 50% of the reduction in whole body glucose disposal [1]. Furthermore, abnormal fatty acid metabolism plays a role in insulin resistance. Excess fat deposition in non-adipose tissue (liver, muscle, pancreatic beta cells) in type 2 DM can be induced by multiple mechanisms such as nutrient excess, which is quite common in insulin resistant individuals, accelerated lipolysis in adipose tissue by insulin resistance, or reduced fatty acid (FA) oxidation (FAO) in mitochondrial defect. Moreover, this increased lipid content, especially in muscle, is linked with insulin resistance [2,3]. As skeletal mitochondrial deficiency was observed in patients with insulin resistance or type 2 DM, it has been proposed as a key player

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in skeletal muscle lipid accumulation [4]. Here, we summarize the causal role of skeletal muscle mitochondria in mediating insulin resistance, with a focus on some recent evidence that mitochondrial dysfunction does not precede insulin resistance.

Molecular mechanism of skeletal muscle insulin resistance: with a focus on links between skeletal muscle mitochondrial dysfunction and lipotoxicity

Tissue-specific insulin sensitivity was first found to decrease in type 2 DM in 1940 [5]. In 1975, diminished ability of insulin to promote glucose uptake in type 2 DM was demonstrated [6]. A following study by DeFronzo revealed markedly decreased whole body glucose disposal during insulin clamp in type 2 DM [7]. As skeletal muscle is a major reservoir for postprandial glucose storage, which accounts for 80% of insulin-stimulated glucose disposal [8], the mechanism of skeletal muscle insulin resistance has been thoroughly investigated. NADH-O2 oxidoreductase and citrate synthase (CS) activity in skeletal muscle of type 2 DM were shown to be decreased, and a concurrent decrease in the size of mitochondria was observed upon electron microscopy [9]. In patients with type 2 DM or prediabetes, decreased expression of oxidative phosphorylation (OXPHOS) genes as well as *NRF-1 and proliferator-activated receptor gamma coactivator 1 (PGC-1) α/β genes*, the master regulators of mitochondrial biogenesis, was observed [10]. A decrease of genes involved in OXPHOS, which was induced by *PGC-1α*, was observed in a subsequent study [11]. Indeed, this decrease was observed not only in subjects with type 2 DM, but also in their lean insulin-resistant offspring, who showed a 30% reduction in mitochondrial OXPHOS based on ^{31}P-magnetic resonance spectroscopy (^{31}P-MRS). Furthermore, this was accompanied by an 80% increase in intramyocellular lipid (IMCL) content [12]. Similarly, the same authors found that mitochondrial density was reduced by 38% and insulin receptor substrate-1 (IRS-1) serine phosphorylation was increased in the muscle of insulin-resistant offspring [13]. Lipid intermediates such as long chain fatty acyl coenzyme A (CoA), diacylglycerols, and ceramides in skeletal muscle are regarded as important regulators of insulin resistance [14]. These intermediates can activate serine/threonine kinases such as protein kinase C in skeletal muscles [15], which then activate phosphorylates serine residues in IRS-1, thereby inhibiting insulin-induced phosphatidylinositol 3-kinase activity. Taken together, mitochondrial deficiency and fat oxidation and the subsequent increase of intramyocellular triglyceride was proposed as a key mediator of insulin resistance [4]. It has also been hypothesized that reduced primary mitochondrial function predisposes one to insulin resistance [13]. Though seemingly very robust and conclusive, questions still arise as to whether increased IMCL is the direct effect of mitochondrial dysfunction and whether IMCL acts as a deleterious factor in insulin sensitivity. Skeletal muscle of trained endurance athletes is markedly insulin sensitive and has a high oxidative capacity, despite having an elevated lipid content [16], and their OXPHOS capacities are not disturbed despite the high IMCL content [17]. These findings suggest that an increased IMCL level is not sufficient to cause mitochondrial damage or insulin resistance. Furthermore, careful consideration is needed when determining whether increased IMCL is the consequence of mitochondrial deficiency/dysfunction or merely derived from increased fat supply, because the possibility that mitochondrial dysfunction is secondary to insulin resistance still resides in this phenomenon.

The latter theory seems to be quite attractive in terms of mitochondrial bioenergetics. The rate of FAO or mitochondrial respiration is not dependent on the rate of fat supply, but rather on energy demand, which is comprised of idling activity plus energy required for adenosine triphosphate (ATP) generation. In other words, under resting condition, when demand for ATP synthesis is decreased, the basal idling activity for protein synthesis, maintenance of membrane potential and proton leaks accounts for most of the mitochondrial energy demand. Skeletal muscle, in general, harbors enormous mitochondrial reserve and can flexibly increase its substrate flux and ATP synthesis according to increases in exercise capacity. Boushel et al. found that skeletal muscle mitochondrial function was normal in type 2 DM, only its number was deficient [18]. As stated above, a 30% reduction in mitochondrial number and OXPHOS capacity is observed in skeletal muscle of type 2 DM. Since mitochondria can flexibly increase its oxidative capacity up to several times during exercise (up to 150 times in very healthy, trained individuals), it can overcome 30% loss of mitochondria or OXPHOS capacity [19]. These findings can also indicate that subtle defects in OXPHOS have little impact on IMCL accumulation because OXPHOS

almost never works at maximal capacity during usual activities. Moreover, as substrate oxidation rate is not dependent on supply, but rather on mitochondrial demand, lipids can accumulate in skeletal muscle when the supply exceeds demand, regardless of its mitochondrial OXPHOS capacity [20].

Collectively, these conflicting results have shown the possibility that insulin resistance might not be governed by skeletal mitochondrial dysfunctions. The following studies introduced here provide some evidence that skeletal muscle mitochondrial dysfunction is not a prerequisite to the development of insulin resistance.

Relationship between mitochondrial function and insulin resistance: preclinical results

A previous *in vitro* study designed to investigate impaired cellular respiratory function by treatment with the mitochondrial inhibitor sodium azide showed, on the contrary to expectations, increased basal glucose uptake, phosphorylation of AMP-activated protein kinase (AMPK) and GLUT4 mRNA expression [21]. Gene manipulation studies in animals have also shown some evidence indicating that skeletal muscle mitochondrial dysfunction does not correlate with insulin resistance. A mouse model with respiratory chain dysfunction in skeletal muscle generated by muscle-specifically knocking-out mitochondrial transcription factor A showed paradoxically increased peripheral glucose disposal during a glucose tolerance test, indicating that mitochondrial dysfunction in skeletal muscle might not be a primary etiological event in insulin resistance [22]. The skeletal muscle specific ablation of PGC-1α in mouse showed that PGC-1α was necessary for normal regulation of mitochondrial gene expression. However, a reduction of PGC-1α levels in skeletal muscle and the subsequent reductions in OXPHOS gene expression were not causally linked to systemic insulin resistance, although of the possibility that PGC-1α and OXPHOS genes contribute to insulin resistance in muscle under other experimental conditions cannot be ruled out [23]. Conditional deletion of apoptosis inhibiting factor (AIF) is known to induce progressive loss of respiratory chain and OXPHOS dysfunction. Muscle- and liver-specific AIF ablation in mice expressing a pattern of OXPHOS were thus generated to look for the relationship between mitochondrial deficiency and insulin resistance. The intervention resulted in paradoxically reduced fat mass and ameliorated insulin sensitivity [24].

Recently, it was shown that heterozygous *Crif1* deletion in the skeletal muscle was not associated with insulin resistance. *Crif1* is a mitochondrial protein required for the intramitochondrial production of mtDNA encoded OXPHOS subunits, and targeted elimination of the *Crif1* gene causes a phenotype that shows organ-specific failure of OXPHOS. These findings supported the hypothesis that skeletal muscle mitochondrial deficiency does not mediate insulin resistance [25]. Collectively, although these gene manipulation studies revealed rather universal results, they require attention during interpretation because they casually reflect extreme cases that might lead to the activation of other compensatory mechanisms. Indeed, in some studies, AMPK level was increased or showed a tendency to increase, which could in turn increase insulin sensitivity, mimicking a "metformin effect." To increase AMPK, ATP content is supposed to be sufficiently inhibited by intervention. However, this phenomenon is less likely to be reproduced in *in vivo* studies of human or animals with insulin resistance.

Relationship between mitochondrial dysfunction and insulin resistance in human type 2 diabetes

Several lines of human studies have also shown that skeletal mitochondrial dysfunction does not act as a direct cause of insulin resistance. In a recent human study, mitochondrial function was measured among three different groups: type 2 DM patients, subjects with impaired fasting glucose, impaired glucose tolerance and/or recently diagnosed type 2 DM, and healthy, normoglycemic controls. *In vivo* mitochondrial function measured by ^{31}P-MRS showed no differences in phosphocreatinine (PCr) and adenosine diphosphate recovery time and maximum aerobic capacity between groups. These findings suggest that mitochondrial dysfunction does not necessarily manifest either cause or consequence of insulin resistance [26]. Another human study showed that, in patients with type 2 DM, mitochondrial respiration was lower than in healthy controls. However, when mitochondrial respiration was normalized for mitochondrial DNA content

or CS activity, there were no differences in OXPHOS or electron transport capacity between patients with type 2 DM and healthy control subjects. The authors concluded that blunting of coupled and uncoupled respiration in type 2 diabetic patients is not attributed to mitochondrial dysfunction, but rather to lower mitochondrial content. It is well known that exercise training increases mitochondrial content in skeletal muscle and aging diminishes mitochondrial OXPHOS capacity; thus, it can be hypothesized that this decreased mitochondrial content may be attributed to sedentary life style and old age in patients with T2DM [18]. Asian Indians are known to have a higher susceptibility to diabetes than Europeans. Thirteen diabetic Indians, 13 nondiabetic Indians, and 13 nondiabetic Northern European Americans were compared. Despite being more insulin resistant, diabetic Indians had similar muscle OXPHOS capacity as nondiabetic Indians, suggesting that diabetes *per se* does not cause mitochondrial dysfunction. Regardless of their diabetic status, Indians had higher OXPHOS capacity than Northern European Americans, although they were substantially more insulin resistant, indicating a dissociation between mitochondrial dysfunction and insulin resistance [27].

The hypothesis that mitochondrial dysfunction acts as a consequence rather than a cause of insulin resistance is further supported by a study showing that, when plasma insulin and glucose concentrations were maintained at similar postabsorptive levels, skeletal muscle ATP production and mtDNA copy numbers were similar in both type 2 diabetic and nondiabetic groups, suggesting that reduced muscle mitochondrial content is not a universal finding in type 2 diabetic patients [28].

The role of high-fat diet in uncoupling of mitochondrial dysfunction from insulin resistance

C57BL/6J mice fed a short-term high fat diet showed altered expression levels of genes involved in a variety of biological processes, including energy metabolism, lipogenesis, and immune function, as well as increased levels of complexes I, II, III, IV, and V of OXPHOS, despite insulin resistance [29]. Another mouse model of free fatty acid challenge showed insulin resistance despite an increase in muscle mitochondria. In this study, activation of peroxisome proliferator-activated receptor (PPAR) δ by fatty acids subsequently increased PGC-1α protein expression in posttranscriptional manner, thereby increasing mitochondrial biogenesis. Mitochondrial DNA copy numbers and mitochondrial enzyme proteins such as CS and cyclooxygenase 1 (COX1) were increased [30]. Additionally, C57BL/6J mice treated with a high fat diet displayed elevated palmitate oxidation rate and palmitoyl-CoA oxidation in isolated mitochondria compared with chow diet controls. High-fat diet groups exhibited significant elevation of PGC-1α and mitochondrial respiratory chain subunits, despite impaired glucose tolerance relative to controls [31]. Rats fed a high-fat diet and given daily injections of heparin to increase free fatty acid levels showed an increase in mitochondrial biogenesis in muscle [32].

An interventional study of one-week treatment of acipimox to lower plasma fatty acid levels paradoxically decreased the PGC-1- and nuclear-encoded mitochondrial genes, despite increasing the glucose disposal rate and insulin sensitivity [33]. Taken together, these results contradict with the preexisting paradigm that reduced FAO mediates lipid-induced insulin resistance. More direct evidence that mitochondrial deficiency is not an etiological event but rather a consequence of insulin resistance was obtained from a study conducted by Bonnard et al. [34]. Mice fed a high-fat, high-sucrose diet (HFHSD) were shown to be glucose intolerant after 4 weeks, but their mitochondrial function was normal. After 16 weeks, these mice were diabetic, and mitochondrial dysfunction occurred, as demonstrated by reduced mitochondrial density and altered structure observed upon electron microscopy, as well as reduced mitochondrial gene expression (Cox1, Cox3, PGC-1α). The results of this study indicated that insulin resistance could be induced by excessive nutrition without preceding mitochondrial dysfunction, and rather, the mitochondria plays as a victim.

Skeletal muscle fat oxidation in insulin resistant humans

If mitochondrial dysfunction is a key player in insulin resistance, the fat oxidation rate should be diminished in insulin resistant or obese subjects. Although the majority of previous studies support this hypothesis, some studies show the oppo-

site results. A previous study of fat metabolism in long-term diagnosed type 2 DM revealed that basal whole body fat oxidation rates were significantly increased compared to controls [35]. Another study showed that mitochondrial function is normal and fat oxidation capacity is increased in both leg and arm muscles in obese humans [36]. Holloway et al. demonstrated that palmitate oxidation was not decreased in skeletal muscle of obese women [37]. Moreover, in a subsequent review, they concluded that obesity itself does not alter the ability of skeletal muscle mitochondria to oxidize fatty acids, and that obesity-related reductions in skeletal muscle FAO can be attributed to reductions in mitochondrial content and not to intrinsic alterations or dysfunction within the mitochondria [38]. Taken together, these findings suggest that mitochondrial dysfunction is not associated with insulin sensitivity.

Incomplete fatty acid oxidation as a cause of insulin resistance

Although a majority of previous reports support the idea that skeletal muscle mitochondrial function mediates insulin resistance, recent findings from animal studies showing that high fat diet induces insulin resistance without exacerbating mitochondrial function or even coordinately increasing mitochondrial biogenesis have made this interpretation puzzling. Thus, the complex relationships between the degree of skeletal muscle FAO and insulin resistance have been investigated. PPAR-α and PPAR-β/δ serve as controllers of the cellular lipid metabolic pathway [39]. Transgenic mice overexpressing PPARα in a muscle specific manner (MCK-PPARα) showed increased beta oxidation and protection from diet-induced obesity compared to controls, but surprisingly, they developed insulin resistance [40]. Conversely, PPARkα nock out (KO) mice were protected from diet-insulin resistance [41]. Interestingly, in this study, AMPK activity was diminished in MCK-PPARα, and AMPK activator 5-aminoimidazole-4-carboxamide ribonucleotide treatment reversed the negative effect of PPARα on glucose transporter (GLUT) 4 expression [41]. This finding led to the possibility that alterations in cellular energetics were involved in glucose intolerant models. Dinitrophenol, a protonophore that uncouples mitochondrial electron transport from OXPHOS, was found to reverse the inhibitory effects of PPARα on expression of GLUT4 and acetyl-CoA carboxylaseα (ACC) phosphorylation. Additionally, skeletal muscle FAO inhibition by oxfenicine improved glucose tolerance in a MCK-PPARα model, despite exacerbated skeletal muscle lipid accumulation. Taken together, these findings have led to revisiting of the Randle effect, which first described the reciprocal allosteric inhibition of glucose metabolism by high-level fatty acid utilization [42].

Inhibition of malonyl-CoA decarboxylase (MCD) results in partial carnitine palmitoyltransferase 1 inhibition. Decreased β-oxidation by MCD KO resulted in protection from insulin resistance after a 12-week high fat diet in mouse models [43]. Conversely, chronic high-fat feeding has been shown to increase the effects of postprandial serum non-esterified fatty acids (NEFAs) and acylcarnitines in serum, and this phenomenon was related insulin resistant states. Even-chain acylcarnitines (C6-C22), which represent incomplete β-oxidation, were increased. This model was marked by increased whole body fat oxidation, impaired switching to carbohydrate substrate during the fasted to fed transition, and coincident reductions in muscle levels of several TCA cycle intermediates. Collectively, the results have shown that obesity, diabetes, and HF feeding are accompanied by increased rather than decreased rates of β-oxidation in skeletal muscle and suppression of mitochondrial fatty acid importation protects against lipid-induced insulin resistance [43].

Chronic high fat feeding can lead to adaptive response in muscle shown as an increase of enzymes involved in FAO; however, this adaptation is not accompanied by parallel increases in enzymes of the TCA cycle. The result of this imbalance is the accumulation of incompletely oxidized metabolites such as acylcarnitines. A more recent study compared plasma concentrations of carnitine and acylcarnitines between fasting, obese nondiabetics and patients with type 2 DM and found that the total summed acylcarnitine concentration and medium-chain acylcarnitines, especially acetylcarnitine levels, were increased in diabetics [44]. Additionally, a positive correlation between acetylcarnitine and glycated hemoglobin level was observed. Moreover, in this study, acylcarnitines activated NFκB in a RAW264.7 cell model, which was previously suggested to promote serine phosphorylation of IRS-1 and thereby play a role in insulin resistance [45]. The authors have hypothesized that reduced mitochondrial number, volume, and mitochondrial substrate oxidation capacity in muscles of type 2 DM might trigger limitation of tricarboxylic acid (TCA) utilization, thereby contributing to inefficient, in-

complete LCFA β-oxidation. However, careful interpretation is required because this was an observational study; therefore, not conclusions regarding whether decreased mitochondrial content is a primary event or secondary to insulin resistance could be made. Taken together, although seemingly conflicting, incomplete FAO arises from an imbalance between increased fatty acid import and/or decreased TCA cycle capacity, and this relatively excessive FAO compared to demand of TCA cycle results in insulin resistance via activation of NFκB.

ROS as a mediator of skeletal mitochondrial dysfunction and insulin resistance

In a recent study, insulin resistance was induced by treatment of TNF-α or dexamethasone in mice. These mice were then treated with two small molecules and four transgenes, each of which were designed to lower ROS levels, and therefore ameliorated insulin resistance [46]. The following study by Bonnard et al. showed that 16 weeks of chronic high sucrose high fat diet (HSHFD) increases protein carbonylation, which is a marker of oxidative stress, whereas at 4 weeks, carbonylation level is not altered. On the other hand, insulin resistance was already observed after providing a HSHFD for 4 weeks [34]. In the same study, streptozotocin-induced mice showed decreased mitochondrial DNA content; however, this was recovered by antioxidant N-acetylcysteine treatment, again suggesting that mitochondrial deficiency is not a primary phenomenon, but rather a response of increased mitochondrial oxidative stress. The following study has suggested that mitochondrial hydrogen peroxide (H_2O_2) emissions serve as a link between excess fat intake and insulin resistance [47]. High-fat diet increases mito- chondrial H_2O_2-emitting potential, while this is prevented by the antioxidant SS31. To specifically determine whether mitochondrial H_2O_2 emissions are a primary factor in the development of diet-induced insulin resistance, transgenic C57BL/6J mice overexpressing human catalase targeted specifically to mitochondria in skeletal and cardiac muscle were evaluated. Scavenging of H_2O_2 by the malonyl CoA-acyl carrier protein transacylase prevented high fat diet induced insulin resistance, which was confirmed by an ameliorated HOMA index and oral glucose challenge test [52]. Mitochondrial function is known to be reduced by the aging process, ultimately leading to muscle insulin resistance. To verify the role of ROS in this process, a mouse model of overexpression of the human catalase gene to mitochondria (MCAT) was designed. In old wild type mice, the p-AMPK/AMPK ratio, p-ACC2 and PGC1α protein levels and mitochondrial density were decreased, and these decreases were recovered in old MCAT mice. The authors hypothesized that mitochondria-generated ROS production decreases AMPK, thereby decreasing mitochondrial biogenesis, resulting in less fat oxidation and finally insulin resistance [48]. More recently, NEFA and insulin treatment in rats were shown to trigger insulin resistance, which was associated with high mitochondrial ROS generation and activation of the NFκB pathway [49]. The ratio of oxidized glutathione (GSSG) to reduced glutathione (GSH) and the superoxide anion production rate were increased. Mitochondrial enzyme activity and ATP production were not impaired by changes in ROS generation under any condition. These findings suggested that skeletal muscle mitochondria plays a small role, at least in acute changes in ROS production rate or insulin resistance caused by high fat diet. Collectively, these studies suggest that ROS is a key mediator of insulin resistance; however, the role of mitochondrial dysfunction is still puzzling. Some studies have indicated that changes in mitochondrial function are negligible in ROS-mediated insulin resistance models [49], while the others showed somewhat substantial decreases in mitochondrial function in subjects with insulin resistance. Fisher-Wellman et al. recently proposed the role of mitochondrial H_2O_2 emission as the primary cause of IR [50]. The main redox buffering system, glutathione (2GSHG/GSSG) and thioredoxin, which are known as “sulfur switches,” derive their reducing power from nicotin amide adenine dinucleotide phosphate and thereby mitigate oxidative stress. However, when mitochondrial supply exceeds demand in response to the chronic high fat diet, mitochondrial H_2O_2 emissions increase, reducing reserve capacity within the redox-buffering system and inducing an oxidative shift in the cellular redox environment. In general, phosphatase activity is decreased during oxidation of redox environments; therefore, stress-sensitive kinases such as c-Jun N-terminal kinase, extracellular signal－regulated kinases, and inhibitors of NFκB can lead to the subsequent Ser/Thr phosphorylation of IRS1, ultimately limiting insulin sensitivity. Taken together, these findings indicate that it is likely that chronic nutrient excess induces mitochondrial overload and increases mitochondrial ROS pro-

duction, and this oxidized mitochondrial environment can disrupt insulin signaling. The mitochondrial dysfunction itself seems to act more as a result of this process than a cause.

CONCLUSION

In recent years, the mechanism of insulin resistance has

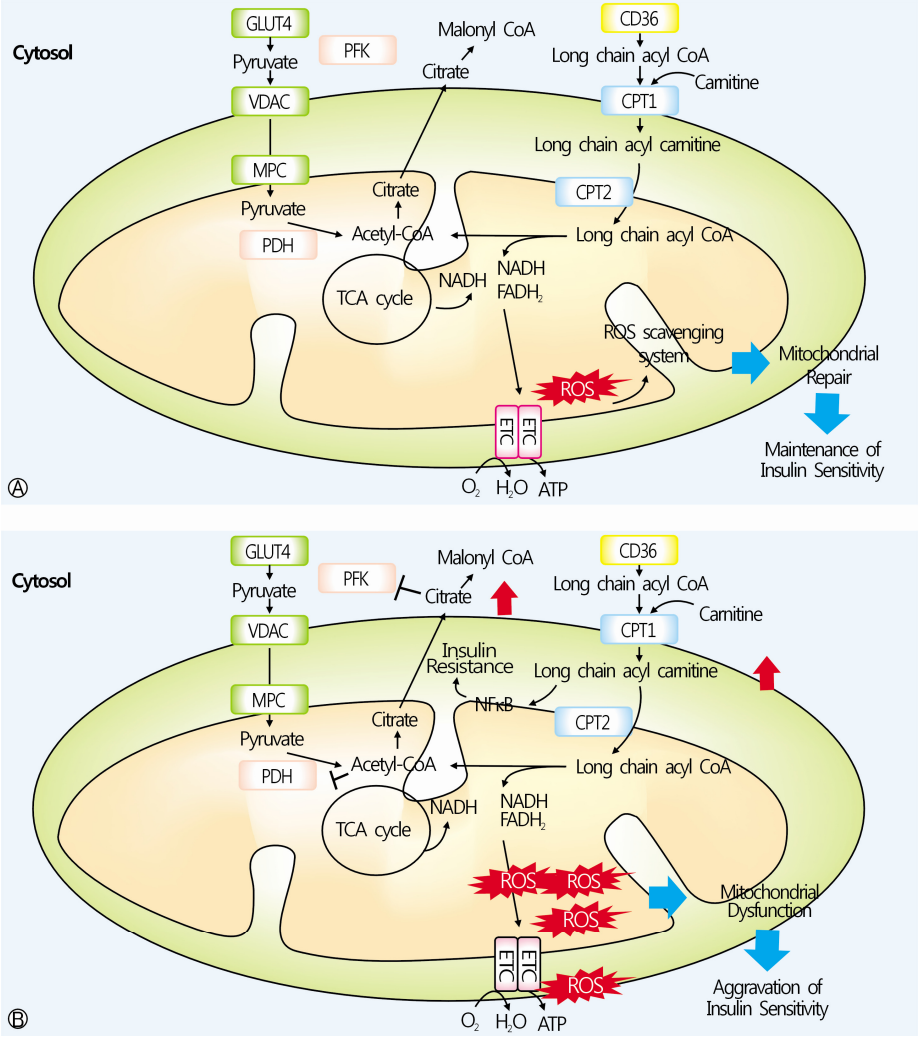

Fig. 1. The impact of mitochondrial nutritional overloading in mitochondrial function and insulin resistance in the skeletal muscle. (A) Under nutritionally homeostatic condition, ROS produced by OXPHOS is readily scavenged by redox buffering system, which maintains mitochondrial function. At the same time, the byproduct of incomplete fatty oxidation such as acylcarnitine is hardly detected. (B) Under nutritionally excess status, especially when FFA influx exceeds mitochondrial capacity to oxidize it, incomplete fatty oxidation occurs, which elicits acylcarnitine abundance. This, in turn, stimulates profinflammtory cytokines such as nuclear factor kappa B which plays a major role in insulin resistance. At the same time, acetyl CoA and citrate derived from exogenous FFA inhibits PDH and PFK, respectively, both of which are critical regulator of glucose uptake and oxidation in the muscle. During OXPHOS, a larger amount of ROS is synthesized which surpasses the capacity of anti-oxidant system. This eventually causes mitochondrial dysfunction that further contributes to insulin resistance. ROS, reactive oxygen species; OXPHOS, oxidative phosphorylation; FFA, free fatty acid; PDH, pyruvate dehydrogenase; PFK, phosphofructokinse; MPC, mitochondrial pyruvate carrier; CD36, cluster of differentiation 36; CPT, carnitine palmitoyltransferase; ETC, electron transport chain; GLUT4, glucose transporter type 4; VDAC, voltage-dependent anion channel.

been widely investigated, and it is rather clear that skeletal muscle mitochondrial deficiency is observed in subjects with insulin resistance or type 2 DM. Although the hypothesis that diminished fat oxidation rate contributes to lipotoxicity has gained wide acceptance, there is also evidence that fat oxidation rate is normal or increased in type 2 DM, and pharmacologic intervention or genetic manipulation that lowers mitochondrial function paradoxically ameliorates insulin resistance. Additionally, incomplete fatty oxidation and mitochondrial redox biology have recently received attention as an attractive mechanism to explain lipotoxicity induced insulin resistance, which supports the notion that mitochondrial dysfunction is not an initiating event (Fig. 1).

Elucidation of the puzzling relationship between skeletal muscle mitochondria and insulin resistance has been challenging because a long asymptomatic period of insulin resistance precedes overt diabetes; therefore, long term longitudinal studies are required to examine such individuals. The mitochondria a dynamic organelle, and its function is affected by various factors such as aging, insulin resistance, sedentary lifestyle, and oxidative stress. These factors are interrelated, making the interpretation more challenging.

Nevertheless, the importance of the mechanism of skeletal muscle insulin resistance should be emphasized, as it may provide promising insight into future therapeutic potential in the treatment of type 2 DM.

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CONFLICT OF INTEREST

The authors have no potential conflict of interest to declare.

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