Is skeletal muscle mitochondrial dysfunction a cause or an indirect consequence of insulin resistance in humans?

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Received 12 November 2008; received in revised form 21 February 2009; accepted 23 February 2009
Available online 5 April 2009

Abstract

The precise cause of insulin resistance and type 2 diabetes is unknown. However, there is a strong association between insulin resistance and lipid accumulation — and, in particular, lipotoxic fatty acid metabolites — in insulin-target tissues. Such accumulation is known to cause insulin resistance, particularly in skeletal muscle, by reducing insulin-stimulated glucose uptake. Reduced fat-oxidation capacity appears to cause such lipid accumulation and, over the past few years, many studies have concluded that decreased mitochondrial oxidative phosphorylation could be the initiating cause of lipid deposition and the development of insulin resistance. The aim of this review is to summarize the latest findings regarding the link between skeletal muscle mitochondrial dysfunction and insulin resistance in humans. At present, there are too few studies to definitively conclude that, in this context, mitochondria are functionally impaired (dysfunction in the respiratory chain). Indeed, insulin resistance could also be related to a decrease in the number of mitochondria or to a combination of this and mitochondrial dysfunction. Finally, we also consider whether or not these aberrations could be the cause of the development of the disease or whether mitochondrial dysfunction may simply be the consequence of an insulin-resistant state.

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Keywords: Diabetes; Human; Insulin resistance; Mitochondria; Skeletal muscle; Review

Résumé

Le dysfonctionnement mitochondrial du muscle squelettique est-il la cause ou la conséquence de la résistance à l’insuline chez l’homme ?

La cause précise de l’insulinorésistance et du diabète de type 2 n’est pas connue. Cependant, il existe une relation forte entre la résistance à l’insuline et l’accumulation de lipides, notamment de métabolites toxiques des acides gras, dans les tissus cibles de l’insuline. Cette accumulation est connue pour induire une insulinorésistance en diminuant l’effet de l’insuline sur le captage du glucose. Une diminution de l’oxydation des lipides semblait être la cause. Durant les dernières années, de nombreuses études ont conclu qu’une diminution de la phosphorylation oxydative, notamment dans le muscle squelettique, pouvait être à l’origine de cette accumulation de lipides et du développement de la résistance à l’insuline.

Le but de cette revue est de faire une synthèse des derniers travaux concernant le lien entre un dysfonctionnement mitochondrial du muscle squelettique et l’insulinorésistance chez l’homme. Actuellement, il existe trop peu d’études pour conclure définitivement que la mitochondrie est réellement défectueuse (défaut du fonctionnement de la chaîne respiratoire). L’insulinorésistance pourrait aussi être liée à une diminution du nombre de mitochondries ou une combinaison des deux phénomènes. Enfin, nous allons aussi discuter si ce dysfonctionnement mitochondrial peut être à l’origine de la résistance à l’insuline ou simplement une conséquence de l’état d’insulinorésistance.

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Mots clés : Diabète ; Homme ; Insulinorésistance ; Mitochondries ; Muscle squelettique ; Revue

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The accumulation of fat in skeletal muscle is correlated with insulin resistance [6,7], and reduction of elevated intracellular triglyceride content in muscle leads to improved insulin sensitivity [15,16]. Paradoxically, in trained athletes, increased muscle fat stores are associated to improved insulin sensitivity [17,18]. More important than triglycerides per se, insulin resistance can be explained by the accumulation of intermediates in fatty acid metabolism such as long-chain acyl-CoA (the metabolically activated form of intracellular fatty acids before beta-oxidation), ceramides (generated from fatty acids) and especially diacylglycerol (an intermediate in the synthesis of triglycerides), which can interfere with the insulin-signalling pathway via activation of serine/threonine kinase and serine phosphorylation of IRS-1 [8–11,19].

However, the mechanisms responsible for the intracellular lipotoxic fatty-derivative accumulation remain open to discussion. On the one hand, it has been shown that the up-regulation of triglyceride synthesis (anabolic pathway) is sufficient to protect skeletal muscle against fat-induced insulin resistance in a mouse model by recreating the paradox seen in athletes [20]. On the other hand, insulin-resistant subjects are characterized by a reduced fat-oxidation rate (catabolic pathway) [3,21]. This means that lipid metabolites can be increased due to an inadequate triglyceride synthesis rate and/or impaired fatty acid oxidation, although the former needs to be confirmed by further clinical studies.

This then begs the question of what cellular defects might explain the reduced fatty acid oxidation seen in the skeletal muscle of insulin-resistant patients. Several studies have reported an increased concentration of malonyl-CoA in the skeletal muscle of insulin-resistant patients with type 2 diabetes [22–24]. Such an increase can lead to decreased fatty acid oxidation by inhibition of carnitine palmitoyltransferase-1 (the rate-limiting step for the entry of long-chain fatty acids into mitochondria) by malonyl-CoA [22]. This results in increased lipotoxic fatty acid metabolites that can, in turn, interfere with the insulin-signalling pathway. Interestingly, under such conditions, it has been suggested that fatty acids that cannot be oxidized (converted to long-chain acyl-CoA) will accumulate in skeletal muscle cells and impair mitochondrial function through lipid peroxidation-induced damage to the mitochondria [25].

In addition, it has been reported that, in insulin-sensitive subjects, increased intracellular fatty acid metabolites can down-regulate the expression of genes encoding for oxidative phosphorylation proteins [26]. Consistent with this, it has been found that increased fatty acid-metabolite concentrations can exert deleterious effects on muscle mitochondrial ATP synthesis by inhibiting the electron transport chain and decreasing the proton motive force [27]. In turn, the reduced mitochondrial oxidative capacity then further exacerbates lipid storage within muscle cells. However, it has also been suggested that reduced fat-oxidative capacity could be due to a mitochondrial defect in insulin-resistant subjects, and that mitochondrial dysfunction is the cause — rather than the effect — of increased fatty acids in skeletal muscle cells [28,29].

In summary, there is evidence of an association between increased intramyocellular lipids (lipotoxic fatty acid
derivatives), mitochondrial dysfunction and insulin resistance. However, it remains to be ascertained as to what is the cause and what is the effect.

1.2. Mitochondrial function and insulin resistance

1.2.1. Data in vivo

Many studies have reported on data obtained in vivo by \(^{31}\)P MRS of skeletal muscle mitochondrial function in type 2 diabetics — and all, regardless of the technique used, have pointed towards impaired oxidative phosphorylation activity.

With one method, for example, mitochondrial oxidative phosphorylation activity was determined by analyzing the saturation transfer between inorganic phosphate and ATP (ATP synthesis flux) in skeletal muscle while at rest. In this case, studies have shown a 30% decrease in ATP synthesis flux in association with lower mitochondrial density in the lean insulin-resistant offspring of patients with type 2 diabetes in comparison to controls subjects matched for age and BMI \([30,31]\). Comparing healthy younger subjects without a family history of type 2 diabetes with healthy elderly subjects (matched for BMI), the same authors reported marked insulin resistance associated with a lower muscle ATP synthesis flux in the elderly population \([32]\).

Interestingly, one study reported no differences in ATP synthesis flux in patients with type 2 diabetes in comparison to their controls, matched for age and BMI, while the ATP synthesis flux was also found to be lower than that of the healthy youngsters \([33]\). However, the authors reported a negative correlation between ATP synthesis and fasting FFA concentration \([33]\). In addition, the age- and BMI-matched controls presented with a higher fasting FFA concentration than the young controls, suggesting that it is primarily lipid availability that leads to deterioration of mitochondrial function \([33]\). Collectively, these findings suggest that the defects in ATP synthesis flux observed in patients with insulin resistance (but no diabetes) may coexist with secondary metabolic events in the overtly diabetic state.

The above-described study was carried out in the fasting state, but another way to study mitochondrial oxidative phosphorylation activity is to apply the same methodology, but under insulin-stimulated conditions that mimic the postprandial state. In this case, it was found that ATP synthesis flux was less stimulated by insulin in the lean insulin-resistant offspring of patients with type 2 diabetes than in the control subjects (matched for age and BMI) \([34]\). Indeed, these results have been recently confirmed in a study in which ATP synthesis flux was significantly increased by insulin in the controls, but not in type 2 diabetes patients \([33]\). Thus, these two studies suggest that the stimulation of ATP synthesis by insulin is altered in the skeletal muscle of insulin-resistant subjects.

A third way to analyze skeletal muscle mitochondrial oxidative phosphorylation in vivo involves measuring PCr resynthesis, or ADP recovery flux, after exercise. During exercise, PCr concentrations decrease and ADP contents increase, with both recovering rapidly after exercise. As recovery is driven mainly by oxidative phosphorylation, the recovery rates reflect mitochondrial capacity — with the slower the rate, the less efficient the mitochondrial activity. When this technique was used in obese type 2 diabetics, their PCr resynthesis rate was lower than in BMI-matched healthy individuals \([35]\). Similar results have been reported by Sirikul et al. \([36]\), who also found that the ADP recovery rate was positively correlated with insulin sensitivity in African-American and Caucasian-American women, suggesting that poorer muscle mitochondrial function among African-Americans may partly explain their lower insulin sensitivity. On the other hand, a recent study found no alterations in PCr and ADP recovery time constants among longstanding, insulin-treated type 2 diabetics, subjects with impaired fasting glucose, impaired glucose tolerance and/or recently diagnosed type 2 diabetes and healthy, normoglycaemic individuals matched for age and body composition \([37]\). However, in that study, the diabetic patients had been taking exogenous insulin treatment for more than five years and continued to take their medication during the study. This suggests that the higher plasma insulin levels in the diabetic group may have been a confounding factor in the measurement of muscle mitochondrial function in vivo. Indeed, insulin is known to affect measurements of mitochondrial function \([38]\).

Nevertheless, taken altogether and regardless of the technique used, these results show that insulin resistance is associated with reduced ATP synthesis in vivo in skeletal muscle mitochondria.

1.2.2. Data ex vivo

Mitochondrial dysfunction may also be explained by an intrinsic abnormality in the respiratory chain or a decreased number of mitochondria, or both. Studies of mitochondrial ATP synthesis (oxidative phosphorylation) ex vivo have involved polarographic respiratory measurements in isolated mitochondria or in permeabilized cells. So far, only two studies have been published that explored mitochondrial function in insulin-resistant patients using such techniques — one in isolated mitochondria and the other in saponin-permeabilized muscle fibres. In the former, the authors found lower ADP-stimulated state-3 (ATP synthesis) and uncoupled-state (maximum respiratory chain activity) oxygen consumption in isolated skeletal muscle mitochondria of type 2 diabetic patients compared with obese non-diabetic controls \([39]\). These results suggest that skeletal muscle dysfunction in diabetic patients could be explained by an impairment in respiratory chain activity. In the latter study, oxygen consumption in the presence of either ADP (state 3) or FCCP (maximum respiratory chain activity) was decreased in permeabilized skeletal muscle fibres in type 2 diabetics \([40]\). However, when these data were normalized for mitochondrial density (mitochondrial DNA or citrate synthase activity), there were no differences in oxidative phosphorylation or respiratory chain activity between patients with type 2 diabetes and healthy control subjects. From this latter study, it appears that skeletal muscle dysfunction in insulin resistance could be attributed to lower mitochondrial content.

However, these discrepancies could reflect the different methods used to assess mitochondrial function. On the one hand, isolated mitochondria lose their interaction with cytoplasm and other cellular structures on being isolated. On the other hand, it is difficult to precisely determine the number of mitochondria with any currently available method. Citrate synthase activity...
and mtDNA are the most frequently used markers of mitochondrial density for determining cell mitochondrial content. However, citrate synthase activity reflects both mitochondrial mass and mitochondrial enzyme activity. In addition, mtDNA content is not necessarily the most accurate marker of mitochondrial mass in skeletal muscle because of the presence of a reticulated network of mitochondria [41].

To summarize, those two studies clearly show that mitochondrial oxidative phosphorylation is impaired in the skeletal muscle of type 2 diabetics. However, whether or not decreases in mitochondrial content or respiratory chain activity, or a combination of both, are contributory to skeletal muscle mitochondrial dysfunction in insulin resistance remain to be ascertained.

1.3. Regulation of mitochondrial function and insulin resistance

Maintaining ATP levels is a critical feature of all cells, and it is known that cells respond to the partial uncoupling of oxidative phosphorylation sufficient to decrease ATP levels by increasing mitochondrial gene expression, and the number and function of mitochondria, so as to replace ATP content [42,43]. This signalling process is largely dependent on PGC-1α, a dominant regulator of mitochondrial function, biogenesis and respiration in many tissues [44–48]; its expression is increased, and the response to uncoupling lost, in animals without it [43]. These results illustrate the fundamental system of energy homeostasis whereby cells and tissues use PGC-1α to restore energy balance. For this reason, it is tempting to speculate that such adaptation — increases in PGC-1α-mediated mitochondrial number and function — could take place in insulin-resistance states in an attempt to reverse decreased ATP synthesis.

PGC-1α is also involved in the transcriptional activity of NRFs that regulate the transcription of genes related to oxidative phosphorylation and stimulate mtTFA, a key transcriptional factor for the mitochondrial genome. On comparing gene expression in skeletal muscle from healthy non-diabetics at low risk of type 2 diabetes (no family history) and those at high risk for type 2 diabetes (positive family history) with diabetic patients, it was found that insulin resistance and type 2 diabetes were associated with reduced expression of the multiple NRF-1-dependent genes encoding key enzymes for mitochondrial function [49,50]. Similarly, PGC-1α was decreased in both diabetic patients and healthy, non-diabetic, offspring of type 2 diabetics [50]. Interestingly, it was reported that levels of PGC-1α mRNA were lower in the skeletal muscle of type 2 diabetes patients compared with insulin-sensitive, lean control subjects, while a three-hour insulin infusion induced an increase in PGC-1α mRNA only in the lean controls [24]. This finding reinforces the idea that the regulation of PGC-1α expression is altered in the skeletal muscle of insulin-resistant subjects.

A more recent study found that PGC-1α mRNA was lower in the skeletal muscle of type 2 diabetics than in their BMI- and age-matched controls [51]. However, none of the genes involved in oxidative metabolism and none of the measured mitochondrial proteins were reduced in the diabetics [51]. Recently, it was found that a modest overexpression of PGC-1α, such as that seen with physiological stimuli, was able to simultaneously increase mitochondrial fuel-handling proteins, fatty acid oxidation and insulin sensitivity in healthy rat skeletal muscle [52]. However, in contrast to these studies, Morino et al. [31] found no changes in PGC-1α, NRFs and mtTFA mRNA levels in the insulin-resistant offspring of type 2 diabetic patients in comparison to their BMI- and age-matched controls. Nevertheless, in this study, mitochondrial content was decreased in the insulin-resistant patients.

Finally, it has been reported that the protein contents of PGC-1α and PGC-1β were not modified in obese women (with an increased homoeostasis model assessment) compared with age-matched lean women [53]. However, the positive association between PGC-1α and palmitate oxidation, and between PGC-1β and cytochrome c oxidase (a component of the mitochondrial respiratory chain), found in lean individuals was lost in the obese women, suggesting that the regulation and/or activity of PGC-1α, rather than PGC-1α protein, is altered by obesity [53].

Altogether, these studies suggest that PGC-1α is not increased to compensate for the decreased mitochondrial function observed in insulin-resistant subjects. On the contrary, the data suggest that PGC-1α might play a role in these abnormalities, and that the expression of genes and proteins involved in mitochondrial function is appropriately down-regulated due to the decrease in PGC-1α level and/or activity and/or regulation. This suggests that there may be a link between the regulation of mitochondrial function and insulin resistance.

1.4. Interventions for mitochondrial function and insulin resistance

One intervention that improves insulin sensitivity in type diabetics is treatment with insulin-sensitizing TZDs, which belong to the class of PPARγ agonists. Of these drugs, rosiglitazone has been found to restore PGC-1α mRNA levels in the skeletal muscle of type 2 diabetic patients [51]. However, the authors could find no differences in mitochondrial gene expression and protein content before and after rosiglitazone treatment [51]. In addition, the same authors recently showed that mitochondrial function (half-time of PCr recovery by MRS) in vivo was not significantly affected by rosiglitazone treatment in type 2 diabetics [54]. However, in this lattermost study, the PCr recovery half-time was correlated with the rosiglitazone-induced decline in fasting plasma insulin and glucose levels. Thus, those in whom the most prominent improvements in mitochondrial function were found also showed the largest decreases in fasting insulin and glucose levels [54]. It has also been reported that pioglitazone activates the gene encoding for PGC-1α in muscle cells, restores insulin signalling, augments the mitochondrial biogenesis programme and restores mitochondrial bioenergetic capacity in insulin-resistant myotubes [55]. Nevertheless, whether or not mitochondria play a key role in the improvement of insulin sensitivity by TZD requires clarification.

Physical activity and/or dietary interventions can restore insulin sensitivity in both insulin-resistant and diabetic subjects [56–59]. Exercise and food restriction are also known to increase mitochondrial content via PGC-1α in healthy

insulin sensitivity was improved [58]. In addition, mitochondrial density and oxidation enzymes were increased, while type 2 diabetic patients, the same authors reported that mitochondrial content appeared to correlate strongly with an intervention—matched for age, weight and physical activity [66]. However, confirming whether or not impaired skeletal muscle mitochondrial function lies behind the lipid accumulation in muscles and further insulin resistance requires more clinical evidence.

1.5. Mitochondria: culprit or victim?

A number of studies suggest that mitochondrial dysfunction is the consequence, not the cause, of insulin resistance. It has been found that, in lean men with low birth weights—an independent risk factor of insulin resistance and type 2 diabetes—plasma glucose and insulin concentrations were elevated while mitochondrial function in vivo was identical to that of matched controls [68]. These findings suggest that mitochondrial dysfunction is not the key defect either explaining or preceding peripheral insulin resistance in those at risk of type 2 diabetes. Interestingly, it was observed that, when plasma insulin and glucose levels were maintained, then (postabsorptive) levels, mitochondrial content and ATP production did not differ between type 2 diabetics and non-diabetics [69]. Such data support the idea that muscle mitochondrial dysfunction in type 2 diabetes is not the leading cause of insulin resistance but, instead, is a functional defect secondary to an impaired response to insulin.

Moreover, it was reported that obese monozygotic twins have lower insulin sensitivity and lower levels of the transcription genes involved in the oxidative phosphorylation pathway in adipose tissue than do their non-obese counterparts [70]. These data suggest that, as low insulin sensitivity and decreased oxidative phosphorylation gene expression are not dependent on the genetic makeup of obese subjects, the defects in mitochondrial function described in type 2 diabetic patients are not inherited. Indeed, in mice fed a high-fat, high-sucrose diet, it was found that mitochondrial defects did not appear before insulin resistance, as no changes were observed in the prediabetic state (after four weeks of the diet) [71]. However, mitochondrial dysfunction was evident in the skeletal muscle of diabetic mice (after 16 weeks of the diet) [71]. Moreover, it was found that the production of ROS was increased in the skeletal muscle of these mice and in cultured muscle cells incubated with high lipid concentrations, and that the latter effects were blocked by antioxidant treatment [71]. This study suggests a critical role for ROS in mitochondrial alterations, while the addition of H₂O₂ induced an antioxidant treatment-sensitive decrease in mitochondrial DNA content and citrate synthase activity in cultured myotubes [71]. Thus, these data demonstrate that mitochondrial dysfunction does not
precede the onset of insulin resistance but is, instead, the result of increased ROS production in skeletal muscle. In line with these findings, it has been reported that, in insulin-resistant cells generated by dexamethasone and TNF-α treatment, ROS are increased [72]. Moreover, when these cells were treated with diverse treatments that are suppressors of ROS, insulin resistance was reduced [72].

ROS are known to alter the function of mitochondria [73]. In addition, it has been reported that increased delivery of fatty acids is closely correlated with oxidative stress in non-diabetic individuals and in various mouse models of obesity [74]. This makes it tempting to speculate that ROS could represent the unifying mechanism that promotes lipid accumulation, insulin resistance and mitochondrial alterations in humans and, therefore, that mitochondrial dysfunction is the consequence — not the cause — of insulin resistance. However, this hypothesis needs more clinical data, as a recent study has reported results that did not favour a role for increased mitochondrial ROS production in the development of insulin resistance [75].

In that clinical study, it was found that physiologically increased plasma FFA concentrations (lipid infusion) reduced insulin-stimulated muscle ATP synthase flux and induced insulin resistance [76]. In addition, it was reported that a three-day high-fat diet decreased the expression of the genes required for mitochondrial oxidative phosphorylation in the skeletal muscle of insulin-sensitive individuals [77]. Interestingly, it was found that healthy subjects treated for a month with stavudine — a nucleoside reverse transcriptase inhibitor (NRTI) known to alter mitochondrial function in human immunodeficiency virus (HIV)-infected individuals — also showed a reduction in skeletal muscle mitochondrial (mtDNA) content [78]. Furthermore, insulin sensitivity was significantly reduced in the stavudine-treated subjects compared with placebo, and was positively correlated with mitochondrial function (as measured by 31P MRS) [78]. These findings suggest that alteration of mitochondrial function may decrease insulin sensitivity in humans. Moreover, it was found that reduced ATP synthesis flux was associated with lower mitochondrial density in the lean insulin-resistant offspring of patients with type 2 diabetes compared with controls who were matched for age and BMI [30,31].

These two studies demonstrate that mitochondrial dysfunction is associated with insulin resistance early in the development of type 2 diabetes, as the offspring of type 2 diabetic sufferers are at an increased risk of developing the disease. Taken together, these findings support the hypothesis that mitochondrial dysfunction is a contributor to insulin resistance, and that alterations in mitochondrial function may play a role in the development of type 2 diabetes.

Fig. 1. Diagrammatic representation of the potential mechanisms involved in insulin resistance in human skeletal muscle. During overfeeding, it appears that fatty acid oxidation is insufficient in the face of increased fatty acid delivery to the cell. As a result, intermediates of fatty acid metabolism (LCA-CoA, ceramides and DAG) accumulate and may interfere with the insulin-signalling pathway, via activation of serine/threonine kinase and serine phosphorylation of IRS-1, thereby causing insulin resistance. Such a decrease in fatty acid oxidation could be due to a PGC-1α-dependent decrease in activity and/or content of mitochondria. Alternatively, malonyl-CoA levels are reported to be increased and could reduce fatty oxidation via inhibition of CPT-1. In turn, fatty acids that cannot be oxidized could be toxic to mitochondria, especially if they react with ROS. Indeed, the resultant lipid peroxidation could cause damage to mitochondrial function. As a result, the altered mitochondrial oxidative capacity would further exacerbate lipid storage within the muscle cell. Interestingly, insulin sensitivity may be improved not only by insulin sensitizers, but also by a combination of physical activity and weight loss — and both in a PGC-1α-dependent manner. Defining the cause-and-effect relationship among the mechanisms linking these events, however, remains to be clarified. CPT-1: carnitine palmitoyltransferase-1; DAG: diacylglycerol; LC-CoA: long-chain acyl-coenzyme A; IRS-1: insulin receptor substrate-1; PGC-1α: PPARγ coactivator-1; ROS: reactive oxygen species; TCA: tricarboxylic acid cycle.
altogether, these data suggest that mitochondrial dysfunction could be an early event in the development of insulin resistance.

Nevertheless, it is difficult to reach any definitive conclusions as to the true sequence of events and whether or not mitochondrial dysfunction is the causal culprit or the victim of insulin resistance. This issue has become even more important as a recent study suggests that there may be exceptions. In some populations, such as Asian Indians, diabetes per se apparently does not cause mitochondrial dysfunction, so the impaired mitochondrial function cannot account for the insulin resistance [79]. It has also been reported that progressive respiratory chain dysfunction (in knockout mice) in skeletal muscle does not result in either diabetes or insulin resistance [80]. In addition, it was found that muscle- and liver-specific AIF ablation in mice initiated a pattern of oxidative phosphorylation deficiency that closely mimicked that of human insulin resistance and, contrary to current expectations, resulted in increased glucose tolerance, a reduced fat mass and increased insulin sensitivity [81].

These data suggest that mitochondrial dysfunction is not the primary causal event in type 2 diabetes and may even result in increased insulin sensitivity as a possible adaptive mechanism. Such a beneficial role for mitochondria in humans remains to be elucidated. On the other hand, mitochondrial dysfunction might be a parallel process that is present concomitant with insulin resistance. Interestingly, both animal and laboratory studies have recently reported that an oversupply of lipids to muscle may be responsible (in addition to an increased production of diacylglycerol and ceramides) for incomplete fatty acid oxidation and that, as a result, lipid-derived intermediates (acylcarnitines, ROS) accumulating in the mitochondria ultimately have led to insulin resistance [82,83]. The authors propose a unifying hypothesis that fits with the data linking insulin resistance to skeletal muscle dysfunction while also suggesting that overloading muscle with energy could be sufficient to launch a distress signal that eventually halts glucose uptake, even when mitochondrial function is normal. Thus, the answer as to whether or not mitochondria are the cause or the effect of insulin resistance is not mutually exclusive, nor should it be surprising that a higher susceptibility to insulin resistance is likely in individuals who have low mitochondrial capacity [84].

2. Conclusion

At present, it is evidently clear that insulin-resistant and type 2 diabetic patients are characterized by several hallmark features: skeletal muscle insulin resistance, altered fatty acid oxidation resulting in elevated intramyocellular lipotoxic fatty acid metabolites and finally dysfunction of mitochondrial oxidative phosphorylation in skeletal muscle (Fig. 1).

However, the precise mechanism linking these events remains to be elucidated. In particular, it is unclear whether altered mitochondria are the cause or the result of a state of insulin resistance. Such a discussion is essential, and it is also important for future research to determine whether or not the use of therapeutic strategies that stimulate skeletal muscle mitochondrial oxidative phosphorylation capacity (mass and/or activity) have any therapeutic potential against insulin resistance and type 2 diabetes.

Conflicts of interest

The authors declare no conflicts of interest with this review.

References


