Biochimica et Biophysica Acta 1840 (2014) 1303–1312

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

Review

The role of mitochondria in the aetiology of insulin resistance and type 2 diabetes ☆

Sheree D. Martin, Sean L. McGee *

Metabolic Remodelling Laboratory, Metabolic Research Unit, School of Medicine, Deakin University, Waurn Ponds 3217, Australia

ARTICLE INFO

Article history:
Received 31 May 2013
Received in revised form 30 July 2013
Accepted 11 September 2013
Available online 20 September 2013

Keywords:
Mitochondrial dysfunction
Insulin resistance
Type 2 diabetes
Lipid accumulation
Reactive oxygen species
Inflammation

ABSTRACT

Background: The prevalence of type 2 diabetes is rapidly increasing world-wide and insulin resistance is central to the aetiology of this disease. The biology underpinning the development of insulin resistance is not completely understood and the role of impaired mitochondrial function in the development of insulin resistance is controversial.
Scope of review: This review will provide an overview of the major processes regulated by mitochondria, before examining the evidence that has investigated the relationship between mitochondrial function and insulin action. Further considerations aimed at clarifying some controversies surrounding this issue will also be proposed.
Major conclusions: Controversy on this issue is fuelled by our lack of understanding of some of the basic biological interactions between mitochondria and insulin regulated processes in the context of insults thought to induce insulin resistance. Aspects that have not yet been considered are tissue/cell type specific responses, mitochondrial responses to site-specific impairments in mitochondrial function and as yet uncharacterised retrograde signalling from mitochondria.
General significance: Further investigation of the relationship between mitochondria and insulin action could reveal novel mechanisms contributing to insulin resistance in specific patient subsets. This article is part of a Special Issue entitled Frontiers of Mitochondrial Research.

1. Introduction

Type 2 diabetes has been labelled as one of the greatest challenges to human health of the 21st century [1]. At present, it is estimated that over 350 million people worldwide suffer from this disease [2]. Most alarmingly, this number is expected to rapidly increase in the future. This disease imparts a huge burden on patients, carers and health care systems and places enormous pressures on national and international economies [1]. Its associated comorbidities, which include cardiovascular disease, stroke, kidney disease and cancer, contribute to ~4 million deaths worldwide each year that are due to type 2 diabetes [3]. With the prevalence of chronic diseases such as type 2 diabetes rapidly increasing, it has been predicted that life expectancies will decline for the first time in over a century [4]. Historically, type 2 diabetes has been perceived as a problem that affects only developed and prospering nations, however new statistics reveal that 80% of people with type 2 diabetes now live in low and middle income countries [5]. These alarming statistics and the increasing prevalence of type 2 diabetes worldwide highlight that few effective treatment strategies exist to combat this disease. This is due, in part, to the fact that aspects of the biology underpinning this disease are poorly understood. Whilst it is known that resistance to the hormone insulin is central to the pathogenesis of type 2 diabetes, the mechanisms driving insulin resistance are not completely understood [6]. Perhaps one of the most contentious issues in the field is whether impaired mitochondrial function is involved in the development of insulin resistance [7,8]. This review will provide an overview of the functional consequences of insulin resistance in various tissues and will examine the available evidence that describes the relationship between mitochondrial dysfunction and insulin action. This will be done in the context of the known roles of mitochondria in various cellular functions.

1.1. Insulin resistance and the pathogenesis of type 2 diabetes

Insulin is a hormone released by β-cells of the pancreas in response to rising blood glucose levels. Insulin activates a canonical signalling

Abbreviations: AgRP, agouti-related peptide; AIF, apoptosis-inducing factor; AMPK, AMP-activated protein kinase; CaMKII, calcium/calmodulin dependent protein kinase II; Cox6a2, cytochrome c oxidase subunit VI peptide 2a; CPT-1, carnitine palmitoyltransferase 1; ETC, electron transport chain; G6Pase, glucose-6-phosphatase; GLUT4, facilitative glucose transporter isoform 4; JNK, c-Jun N-terminal kinase; MICU1, mitochondrial Ca^{2+} uptake 1; MMP, mitochondrial membrane potential; MPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; Myo1c, myosin-1c; NCLX, $Na^{+}/Ca^{2+}/Li^{+}$ exchanger; Nox, NADPH oxidase; NPY, neuropeptide Y; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1α, peroxisome proliferator-activated receptor coactivator 1 alpha; POMC, proopiomelanocortin; PTEN, phosphatase and tensin homolog; PTP, protein tyrosine phosphatase; ROS, reactive oxygen species; TCA, tricarboxylic acid; Tfam, transcription factor A mitochondrial; TNFα, tumour necrosis factor alpha; TXNIP, thioredoxin-interacting protein

☆ This article is part of a Special Issue entitled Frontiers of Mitochondrial Research.

* Corresponding author at: Metabolic Remodelling Laboratory, Metabolic Research Unit, School of Medicine, Deakin University, Pigdons Rd., Waurn Ponds, Victoria 3217, Australia. Tel.: +61 3 5227 2519; fax: +61 3 5227 2945.
E-mail address: sean.mcgee@deakin.edu.au (S.L. McGee).

0304-4165/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbagen.2013.09.019

pathway (see [9] and [10] for reviews) that regulates numerous cellular effects in many different target tissues. A primary function of insulin is to facilitate nutrient uptake and storage in states of nutrient excess, such as after a meal [9]. Insulin is also able to control feeding behaviour and energy expenditure via specific brain centres [11]. These diverse functions make insulin critical for the integration of whole body metabolism with nutrient availability and demand.

Therefore, insulin resistance has numerous detrimental effects on metabolism that are the basis for a number of chronic diseases, including type 2 diabetes. Insulin resistance impairs glucose uptake into skeletal muscle, primarily due to the defective regulation of the facilitative glucose transporter isoform 4 (GLUT4) facilitative glucose transporter [12]. Insulin stimulation of skeletal muscle normally results in translocation of GLUT4 containing storage vesicles from intracellular sites to the sarcolemma, where the GLUT4 protein is then inserted into the membrane to facilitate glucose transport into the muscle cell [13]. Whilst the exact defect in this process in insulin resistant states has yet to be definitively established, and is likely to be multifaceted in heterogeneous forms of insulin resistance, impaired glucose uptake has significant effects on whole body glucose homeostasis. Indeed, skeletal muscle accounts for ~80% of post-prandial glucose disposal in healthy individuals [14]. In the liver, suppression of glucose output is impaired in the insulin resistant state, due to impaired suppression of gluconeogenesis and glycogenolysis [15]. Again, the exact mechanisms mediating this defect are not yet completely resolved, but are thought to include transcriptional dysregulation of the key gluconeogenic enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase; [16]). Whilst insulin resistance in skeletal muscle and the liver has negative effects on glucose homeostasis, the major impact of insulin resistance in adipose tissue is impaired suppression of lipolysis, which contributes to the hyperlipidaemia seen in insulin resistant states [17]. This is most detrimental in visceral adipose tissue and is also thought to alter the secreted adipokine profile to a pro-inflammatory state, which in turn has detrimental systemic effects on numerous metabolic tissues [18]. The heart is also susceptible to insulin resistance and this is associated with altered substrate metabolism, which similar to skeletal muscle, involves defective GLUT4 translocation to and/or insertion into the plasma membrane [19]. This results in a shift towards fatty acid oxidation at the expense of anaerobic and oxidative glucose metabolism, which can drive morphological and functional alterations in the heart [19]. Resistance to insulin can also occur in the satiety centres of the hypothalamus, such as the arcuate nucleus [20]. Insulin signalling in the arcuate increases proopiomelanocortin (POMC) expression, whilst reducing neuropeptide Y (NPY)/agouti related peptide (AgRP) expression, which via neuropeptide signalling to secondary neuronal nuclei, reduces food intake and enhances energy expenditure [20]. Insulin resistance in these centres, therefore, contributes to hyperphagia and reduces energy expenditure.

Together, these features of insulin resistance in multiple tissues are also hallmark features of type 2 diabetes. Indeed, the hyperglycaemia and hyperlipidaemia associated with insulin resistance are thought to be responsible for many of the co-morbidities associated with type 2 diabetes [21]. As insulin resistance appears central to the development of type 2 diabetes, intense research efforts have been dedicated to understanding its molecular mechanisms. This research effort suggests that the development of insulin resistance is multifactorial and involves complex interactions between the environment and genetic susceptibility [22]. At a mechanistic level, ectopic lipid accumulation in non-adipose tissues, chronic low grade systemic inflammation, endoplasmic reticulum stress and altered gut microbiome have all been implicated in the development of insulin resistance [23]. However, numerous associative studies have identified links between impaired function of mitochondria, the organelle responsible for the majority of cellular ATP production, and the development of insulin resistance in multiple tissues. The following sections will describe the role of mitochondria in normal cellular function and review the evidence that implicates mitochondrial dysfunction in the development of insulin resistance.

2. Major cellular processes regulated by mitochondria

Mitochondria regulate numerous cellular processes and are a critical contributor to cellular and organismal homeostasis. This section will review some of the major processes in which mitochondria are involved and will provide a superficial framework for understanding potential links between mitochondrial dysfunction and insulin resistance.

2.1. ATP production

Mitochondria are the primary site of cellular ATP production, accounting for up to ~90% of all ATP produced depending on tissue type [24]. Aerobic ATP production uses a network of proteins, termed the electron transport chain (ETC), which couples formation of an electrochemical gradient with oxidative phosphorylation to produce ATP from ADP [25]. The proteins of the ETC reside in the inner mitochondrial membrane, which surrounds the mitochondrial matrix. The matrix is the site of the tricarboxylic acid (TCA) cycle, a fundamental metabolic pathway that oxidises metabolites derived from carbohydrates, lipids and proteins [26]. The citric acid cycle oxidises acetyl-CoA producing NADH and FADH2, intermediate high-energy electron carriers that donate electrons for the redox reactions of the ETC, which consists of four protein complexes (I, II, III, and IV; [25]). Complexes I and II accept electrons from NADH and $FADH_2$ respectively, which are then passed to subsequent complexes down a favourable reduction potential gradient. Molecular oxygen is used as the terminal electron acceptor at complex IV [27]. The exergonic nature of these reactions is used to pump protons out of the matrix by complexes I, III and IV, into the inter-mitochondrial membrane space, resulting in the formation of a proton gradient across the mitochondrial membrane [27]. This proton gradient is utilised by ATP synthase (also termed complex V), which allows protons to flow back into the mitochondrial matrix down their concentration gradient, using the energy released from this reaction to drive oxidative phosphorylation of ADP to form ATP [27].

Normal mitochondrial function is a complex interaction between respiration, or oxygen consumption by complex IV, mitochondrial membrane potential (MMP), leak of protons across the inner mitochondrial membrane, leak of electrons from the ETC in the form of reactive oxygen species (ROS), substrate supply and energy demand [28]. Basal mitochondrial respiration is comprised of two components — consumption of molecular oxygen that is coupled to ATP production and oxygen consumption that is linked to proton leak across the inner mitochondrial membrane, which is termed uncoupled respiration [29]. Although dependent on cell/tissue type, respiration coupled with ATP production is generally the largest quantitative contributor to basal mitochondrial respiration [29], and is primarily driven by energetic demand, in the form of local ADP concentration, rather than substrate supply [30]. The interactive nature of mitochondrial function is highlighted by the interplay between the effects of uncoupled respiration on ATP production. Assuming constant total respiration, increased uncoupled respiration reduces the mitochondrial membrane potential, ATP synthase activity and ATP production [29]. Furthermore, the decrease in mitochondrial membrane potential associated with uncoupled respiration can reduce ROS production, which primarily occurs at complexes I and III and is often driven by elevated mitochondrial membrane potential [31]. The complex interaction between these indices of mitochondrial function highlights the importance of measuring many of these parameters to completely understand the response of mitochondria to particular insults or physiological challenges.

2.2. Apoptosis

Mitochondria are also intimately involved in the regulation of apoptosis, or programmed cell death [32]. Characteristics of apoptosis

include chromatin condensation and nuclear fragmentation, blebbing of the plasma membrane and cell shrinkage [32]. Apoptosis plays an essential role in a vast array of cellular processes including development and ageing, regulation of normal cell turnover and proper development and function of the immune system [33]. Mitochondria control intrinsic apoptosis through regulated mitochondrial permeability transition pore (MPTP) opening and release of cytochrome c [34]. The release of cytochrome c is governed by proteins of the Bcl-2 family, which are localised to mitochondrial membranes [32]. Apoptotic signalling converges to the Bcl-2 family of proteins and alters their physical interactions, which contributes to MPTP opening, cytochrome c release and activation of caspases, a family of intracellular cysteine proteases, to facilitate cell death [35]. Induction of intrinsic apoptosis also affects other aspects of mitochondrial function. For example, MPTP opening also reduces the MMP, which can impair mitochondrial ATP production and in cases where MMP is non-existent can also result in increases in ROS production due to a mismatch between ETC reduction state and MMP that fails to drive oxidative phosphorylation [36]. The permeability of the outer mitochondrial membrane governed by the MPTP can also result in the release of other mitochondrial proteins in addition to cytochrome c, and provides another mechanism by which mitochondrial function can signal to other compartments of the cell [37].

2.3. Calcium homeostasis

Mitochondria also play a key role in cellular calcium (Ca^{2+}) homeostasis through regulated Ca^{2+} influx and efflux [38]. Mitochondrial Ca^{2+} regulation plays a key signalling role in cellular processes ranging from ATP production to cell death [38]. The tight control of cellular Ca^{2+} levels is imperative for its role in numerous signal transduction pathways as a second messenger [39]. Cellular Ca^{2+} also regulates flux through a number of metabolic pathways, including oxidative phosphorylation [40]. Therefore, regulation of Ca^{2+} homeostasis is critical for normal cell function and the mitochondria's ability to store and release Ca^{2+} is important in this regulation.

The influx of Ca^{2+} into the mitochondria is determined by the cytosolic Ca^{2+} concentration, the concentration of Ca^{2+} in the mitochondrial matrix and the membrane potential across the mitochondrial inner membrane [41]. Mitochondrial Ca^{2+} uptake is mediated by a mitochondrial Ca^{2+} uniporter (MCU) termed the mitochondrial Ca^{2+} uptake 1 (MICU1), which consists of two transmembrane domains that likely form a gated ion channel in the mitochondrial inner membrane [42]. The pathway of mitochondrial Ca^{2+} efflux involves H^+/Ca^{2+} and Na^+/Ca^{2+} exchangers. The Na^+/Ca^{2+} exchanger was identified as the $Na^+/Ca^{2+}/Li^+$ exchanger (NCLX) and is located on the mitochondrial inner membrane [43]. This exchanger allows for Na^+ and Li^+-dependent mitochondrial Ca^{2+} release and has ubiquitous expression in most cell types examined, but is particularly active in excitable cells, such as cardiac cells [41]. In contrast, the H^+/Ca^{2+} exchanger has been found to be prominent in nonexcitable cell types, and less is known about its molecular identity. The Ca^{2+} efflux facilitated by these exchangers prevents excessive Ca^{2+} accumulation in the mitochondrial matrix and subsequent loss of the membrane potential of the inner mitochondrial membrane [44]. However, there is potential for the rate of Ca^{2+} influx to exceed the rate of efflux resulting in Ca^{2+} overload, which can alter mitochondrial function. Excessive Ca^{2+} in the mitochondrial matrix can lead to prolonged opening of the MPTP, thus increasing the permeability of the inner mitochondrial membrane [45]. This results in depolarisation of the inner mitochondrial membrane, cessation of oxidative phosphorylation and a subsequent cascade of events, including the release of apoptotic factors and cell death [46]. In contrast, transient Ca^{2+}-dependent MPTP opening has been proposed as a method for fast release of Ca^{2+} from the mitochondrial matrix to prevent overload, maintain Ca^{2+} homeostasis and protect against cell death [45].

3. Associations between mitochondrial function and insulin resistance

Numerous observations have made an association between mitochondria, insulin resistance and type 2 diabetes, which have typically been centred on reductions in mitochondrial capacity and/or function in insulin resistant or diabetic patients and animal models. This section will review the evidence linking impaired mitochondrial capacity and/or function with insulin resistance in a number of key metabolic tissues.

3.1. Skeletal muscle

From a historical perspective, some of the first observations that impaired mitochondrial function and/or capacity are associated with insulin resistance were made in skeletal muscle. Patients with mitochondrial myopathies also manifest peripheral insulin resistance and glucose intolerance, and phenocopy a number of aspects of muscle in the diabetic state, such as lipid and glycogen accumulation [47–49]. Whilst there are also profound neuroendocrine abnormalities in most cases of mitochondrial myopathy, in the mid- to late 1990s, it was first found that the skeletal muscle of type 2 diabetes patients was characterised by impaired oxidative capacity for both glucose [50] and lipids [51] and was related to mitochondrial oxidative capacity [52]. The finding that type 2 diabetes is associated with reduced oxidative capacity has been replicated in numerous human and animal studies. Contention exists over whether this reduced mitochondrial oxidative capacity is attributed to reduced mitochondrial density [53,54] and/or reduced oxidative phosphorylation capacity per mitochondria [55,56]. A study by Ritov et al. [55] found a reduction in electron transport chain activity in the subsarcolemmal mitochondrial fraction of muscle biopsies from obese and type 2 diabetic patients. Mitochondrial content, as measured by mitochondrial DNA (mtDNA), was also lower in both groups yet this loss was not thought to fully account for the decrease in electron transport chain activity. Boushel et al. [54] measured mitochondrial O_2 flux capacity in permeabilised muscle fibres from biopsy samples and found that decreases in O_2 flux capacity in type 2 diabetic patients were lost when normalised for mtDNA content or citrate synthase activity. However, in comprehensive studies of skeletal muscle from diabetic patients both in vivo and ex vivo, Phielix et al. [57] showed that ADP-stimulated respiration and maximal respiratory capacity were reduced in diabetic patients by 35% and 31% respectively, independent of altered mitochondrial content. Furthermore, in vivo mitochondrial function was reduced by ~25% in these same patients. These findings suggest that intrinsic defects in mitochondrial function occur in type 2 diabetes. The origin of the mitochondrial phenotype observed in insulin resistant and type 2 diabetic patients has also been thoroughly examined. The overall conclusions drawn from these studies are that the impairments in mitochondrial capacity and/or function are not genetically acquired, but are rather due to environmental factors [58–60]. A number of studies have subsequently reported that physical inactivity is the major contributor to the mitochondrial defects observed in the skeletal muscle of diabetic patients [61,62].

Whilst the exact nature of the mitochondrial impairment has been debated, so too has been whether the defect in mitochondrial oxidative capacity is a cause or consequence of insulin resistance. Evidence that potentially supports a role for impaired mitochondrial oxidative capacity as a driver of insulin resistance has come from studies involving asymptomatic first degree relatives of diabetes patients. Although these subjects were not diabetic, these studies have consistently showed that these subjects also share defects in mitochondrial oxidative metabolism. For example, insulin resistant offspring of patients with type 2 diabetes showed a ~30% reduction in mitochondrial phosphorylation when compared with normal subjects [63]. A potential biological explanation for this phenomenon has been posited based on the finding that non-diabetic subjects with a family history of the disease

had reduced expression of peroxisome proliferator-activated receptor coactivator 1 α (PGC1α), a nuclear-encoded transcriptional coactivator that is a key regulator of mitochondrial biogenesis, and multiple mitochondrial genes [64]. Similar findings were observed in type 2 diabetes patients [65]. As skeletal muscle PGC1α expression is exquisitely sensitive to exercise and activity levels [66], reduced PGC1α expression in insulin resistant and diabetic patients could be the link between inactivity and the mitochondrial phenotype in these patients. However, another study showed that insulin resistant offspring of patients with type 2 diabetes did not have reduced expression of PGC1α mRNA or protein, but did have decreased mitochondrial density of 38% as measured by electron microscopy [67]. Also, normo-glycemic first degree relatives of type 2 diabetic patients were found to have comparable skeletal muscle PGC1α mRNA levels as control subjects [68]. In addition, gain of function studies have reported conflicting data on the role of PGC1α in the aetiology of insulin resistance [69]. Consequently, the biological mechanisms responsible for the impaired mitochondrial capacity and/or function in insulin resistant patients remain elusive.

These observational studies have not resolved however, whether mitochondrial dysfunction precedes insulin resistance. Other approaches have been used in an attempt to delineate whether mitochondrial dysfunction is a driver of insulin resistance in humans. For example, studies in elderly subjects that were matched with young subjects for body weight and composition revealed that insulin resistance was associated with a 40% reduction in skeletal muscle mitochondrial ATP synthesis [70]. Whilst these elderly subjects were insulin resistant, they were not classified as diabetic, which suggests that the association between impaired mitochondrial function and insulin resistance is not dependent on the progression to type 2 diabetes. This is consistent with reduced mitochondrial ATP synthesis in insulin resistant offspring of diabetic patients that do not yet have diabetes [63]. Indeed, obese and insulin resistant, but non-diabetic subjects also showed evidence of reduced skeletal muscle mitochondrial content [71]. Interestingly, this was evident in intermyofibrillar mitochondria, but not sub-sarcolemmal mitochondria [71]. Weight loss has also been examined in an effort to tease out whether there is a causal relationship between mitochondrial dysfunction and insulin resistance. Many of these studies have showed a disconnection in this relationship [72–74]. For example, caloric restriction-induced weight loss that enhanced insulin action and reduced skeletal muscle lipids was associated with no change in mitochondrial enzyme activities and reduced mitochondria size [74]. This could suggest that impaired mitochondrial function is not a key determinant of insulin action. Although these studies have enhanced our knowledge of the insulin resistant phenotype, they have not provided definitive answers on whether impaired mitochondrial function is central in the development of insulin resistance.

Well controlled time course studies in rodent models have been performed in an effort to determine whether impaired mitochondrial function precedes the development of insulin resistance. Conclusions drawn from these studies typically show that detectable alterations in mitochondrial morphology occur after the onset of insulin resistance [75]. An obvious limitation to these studies is that in the context of heterogeneous forms of insulin resistance, the conclusions drawn are likely limited to the model being studied. Indeed, there are pronounced differences in the mitochondrial phenotypes of obese rodents and humans. For example, diet-induced obesity in specific strains of mice and rats increases mitochondrial gene expression and the capacity for mitochondrial fatty acid oxidation [76], whilst obese humans have reduced mitochondrial gene expression and capacity for fatty acid oxidation [77]. Another complicating factor when comparing many of these studies is that they have not standardised measures of mitochondrial function, making it difficult to determine whether a true functional deficit exists. Genetic models of mitochondrial impairment have also added to the controversy regarding the involvement of mitochondria in the development of insulin resistance. For example, mice with muscle- and liver-specific ablation of apoptosis-inducing factor (AIF), a component of complex I, which leads to an oxidative phosphorylation deficiency similar to that found in the human insulin resistant state, had increased insulin sensitivity and resistance to diabetes and obesity [78]. Furthermore, ablation of cytochrome c oxidase subunit VI peptide 2a (Cox6a2; [79]) and iron-containing enzymes of the ETC [80] also protects against insulin resistance. So too does deficiency of transcriptional regulators of mitochondrial biogenesis, such as mitochondrial transcription factor A (Tfam; [81]) and the PGC1 family of transcriptional coactivators [82]. The mechanisms mediating these effects remain unknown, however a number of factors should be considered in interpreting these studies. Indeed, complete gene ablation is a non-physiological model of mitochondrial dysfunction that could result in permanent shifts in substrate metabolism that would not otherwise be observed in vivo. Many of the conclusions drawn from this collection of studies also assume that ablation of proteins with very different functions within the ETC results in a homogenous form of mitochondrial dysfunction. As previously highlighted, the dynamic and interactive nature of various components of normal mitochondrial function suggests that divergent impairments in the ETC could result in different forms of mitochondrial dysfunction. Some of these studies have also included models of whole body gene knockout, and as the exact role of mitochondrial dysfunction in various metabolic tissues has not yet been determined, nor the role of tissue cross-talk in this context, these data are difficult to interpret.

Hence, although it is well established that there is a correlation between impaired mitochondrial function in skeletal muscle and type 2 diabetes, the absolute requirement for mitochondrial dysfunction in the development of insulin resistance is questionable. However, it is possible that mitochondrial dysfunction is sufficient for insulin resistance in specific insulin resistance subtypes. Patients with mutations in mitochondrial DNA that impair mitochondrial function and are insulin resistant are a good example of this. There remain many unanswered questions as to the specific mechanisms that might mediate these effects. Furthermore, it is unclear whether the findings observed in skeletal muscle can be applied to other insulin-sensitive tissues that have markedly different metabolic functions.

3.2. Adipose, the liver and heart

The role of adipose tissue in the development of whole body insulin resistance is complex, with the site of the adipose depot being an important factor in the pathogenesis of insulin resistance. A wealth of evidence suggests that dysfunction of visceral adipose tissue is more closely associated with insulin resistance and the development of type 2 diabetes than dysfunction of subcutaneous adipose tissue [83]. For example, impaired suppression of lipolysis and adipokine release in visceral tissue is thought to play a major role in the aetiology of insulin resistance, whilst expansion of subcutaneous adipose tissue has been proposed to be somewhat protective by acting as a sink for free fatty acids and glucose [84]. It has been established that there is a clear link between insulin resistance and reduced mitochondrial capacity/function in both visceral and subcutaneous adipose tissues. Markers of mitochondrial capacity, including gene expression, are reduced in the visceral epididymal fat pad of *ob*/*ob* mice [85]. Similar findings have been observed in the subcutaneous inguinal fat pad of *db*/*db* mice [86,87]. However, the functional significance of this mitochondrial defect in adipose tissue is unknown, and could be markedly different in various adipose depots based on their proposed role in the development of insulin resistance. Functional insights into the role of adipose mitochondria have been gleamed from studies with anti-diabetic agents. Treatment of diabetic mice with the anti-diabetic drug rosiglitazone increased the expression of mitochondrial genes and improved mitochondrial function [85–87]. Similarly, treatment of human subjects with pioglitazone showed similar improvements in mitochondria, in subcutaneous adipose tissue [88]. Notwithstanding the associative nature of

these studies, these data could suggest that improvements in adipose mitochondrial function are linked with improved whole body insulin action. These findings are not only restricted to anti-diabetic drugs, as another study in a rodent model of insulin resistance and type 2 diabetes showed that physical activity normalised white visceral adipose tissue mitochondrial content and improved glucose homeostasis [89]. Despite these associative findings, the causality of the relationship between adipose mitochondrial dysfunction and the development of insulin resistance has also been questioned by observations that reduced mitochondrial content in visceral white adipose tissue occurs after the development of hyperglycaemia [89,90]. Together, these studies highlight that the contentious role of mitochondria in insulin resistance is not restricted to skeletal muscle.

Despite the central role of the liver in whole body glucose homeostasis and insulin action, there are few studies that have examined the role of hepatic mitochondrial dysfunction in insulin resistance and type 2 diabetes. Of course, such data from human subjects is extremely scarce as tissue biopsy samples are limited. However, a study by Szendroedi et al. [91] found that patients with type 2 diabetes had reduced absolute hepatic ATP concentrations as well as inorganic phosphate levels, which were associated with hepatic but not peripheral insulin resistance. A follow-on study by the same group showed that type 2 diabetic individuals had reduced hepatic ATP turnover at rest that correlated positively with both peripheral and hepatic insulin resistance [92]. Intriguingly, these observations correlated negatively with waist circumference, BMI and fasting plasma glucose, which could suggest that greater complexity underlies the involvement of hepatic mitochondrial dysfunction and integration of whole body energy homeostasis [92]. An association between hepatic mitochondrial dysfunction and insulin resistance has also been observed in animal models. A recent study by Bouderba et al. [93] of *Psammomys obesus*, a polygenic animal model of type 2 diabetes, found that diabetic animals had reduced oxidative capacity in isolated mitochondria from the liver. The scarcity of data in this area highlights the need for further studies into the role of mitochondrial dysfunction in the liver in the aetiology of insulin resistance and type 2 diabetes.

Although there are many studies examining mitochondrial function in the type I diabetic heart, this is not the case for type 2 diabetes, where studies are somewhat limited by comparison. Two initial studies examined mitochondria isolated from the *db*/*db* heart, finding dysfunctional oxidative metabolism and reduced pyruvate dehydrogenase activity [94,95]. Further studies observed increased fatty acid oxidation associated with increased myocardial oxygen consumption and decreased cardiac efficiency in rodent models of obesity and type 2 diabetes [96–98]. Boudina et al. [99] showed that mitochondrial oxidation and ATP synthesis were uncoupled by fatty acids in the *db*/*db* heart and likely contribute to these metabolic deficiencies. Another study by the same group examined the direct contribution of impaired insulin signalling to altered mitochondrial respiration and found that mice with a cardiomyocyte deletion of insulin receptors had increased uncoupled respiration [100]. Supporting a central role for mitochondrial dysfunction in diabetic cardiomyopathy comes from a study that administered the anti-oxidant metallothionein, which restored cardiac function in a model of diabetes [101]. However, the exact role of mitochondria in this response has not been completely resolved. From these few studies, the involvement of mitochondrial abnormalities in the pathophysiology of the insulin resistance in the diabetic heart remains unclear [102].

4. Potential mechanisms linking impaired mitochondrial function and insulin resistance

The complex nature of mitochondrial function and the various putative defects in mitochondria in insulin resistant and diabetic states have led to the development of a number of theories describing the mechanisms linking mitochondria and insulin resistance. This section will discuss the most common theories posited to explain this relationship.

4.1. Ectopic lipid accumulation

A number of theories describing potential mechanistic links between mitochondria and insulin resistance have been proposed since the first discoveries that impaired mitochondrial function and/or capacity are associated with insulin resistance (Fig. 1). Initial theories proposed that impaired mitochondrial capacity results in compromised lipid oxidation, which in turn leads to ectopic tissue lipid accumulation [103]. In particular, increases in specific lipid metabolites such as ceramides and diacylglycerol have been linked to activation of kinases, such as Protein Kinase C isoforms, which can impair insulin signalling, most notably at the level of the insulin receptor substrates (IRS; [104]). This theory has been supported by interventionist studies where rates of fatty acid oxidation have been increased with a resultant protection against insulin resistance. For example, skeletal muscle overexpression of carnitine palmitoyltransferase 1 (CTP-1), the transporter responsible for fatty acid import into the mitochondria, enhances fatty acid oxidation and preserves insulin sensitivity [105]. A number of counter arguments to this theory have been put forth, however. Firstly, many insulin resistance states, such as that observed with diet-induced obesity in rodents for example, are associated with increased fatty acid oxidation and an increase in the capacity of mitochondria to oxidise fatty acids [76]. Whilst there have been few human studies to replicate these findings, they suggest that impaired mitochondrial capacity for fatty acid oxidation is not universally required for insulin resistance. Secondly, skeletal muscle maximal mitochondrial respiratory capacity is often many-fold higher than basal respiration rates [106]. The large spare respiratory capacity of skeletal muscle mitochondria is required for the large ATP demand associated with muscle contraction, but suggests that a relatively small reduction in respiratory capacity should not impact basal fatty acid oxidation. However, it is unclear whether this is also true for other cell/tissue types. The idea that mitochondrial capacity should impact on fatty acid oxidation also ignores basic principles of bioenergetics, which states that ATP demand, rather than the oxidative capacity for substrates, is the primary determinant of mitochondrial flux and substrate oxidation rates [28]. Thirdly, a number of studies have shown that reducing fatty acid oxidation by mitochondria can actually protect again the development of insulin resistance. It has been proposed that in states of fatty acid oversupply, incomplete fatty acid oxidation can result in accumulation of lipid metabolites that have inhibitory effects on insulin action [107]. Finally, it has been shown that insulin resistance can occur independently of defects in insulin signalling at the level of IRS proteins [108]. Whilst this does not necessarily preclude lipid-mediated insulin resistance due to reduced mitochondrial capacity as a valid mechanism, it does cast doubt over the proposed molecular mechanisms involved and also suggests that insulin resistance is heterogeneous in nature and multifactorial. These arguments are further confounded by recent evidence that mitochondrial capacity in human diabetic subjects is most closely related to inactivity, rather than an intrinsic mitochondrial defect, either genetic or environmental [62]. This could be interpreted that mitochondria in these subjects adapt to the energetic requirements demanded of them and that energy imbalance is the major driver of insulin resistance, which would contribute to ectopic lipid accumulation in the absence of an intrinsic defect in mitochondrial function.

4.2. Reactive oxygen species (ROS) production

More recently, ROS production by mitochondria has emerged as a link between mitochondria and insulin action (Fig. 1). Redox balance is known to play a critical role in cellular homeostasis, however imbalances in redox state are also associated with a number of dysfunctional cellular processes. A universal link between ROS and insulin resistance was first recognised by Houstis et al. [109], who showed that antioxidants could prevent multiple, notionally heterogeneous forms of cellular insulin resistance. Administration of these same antioxidants to

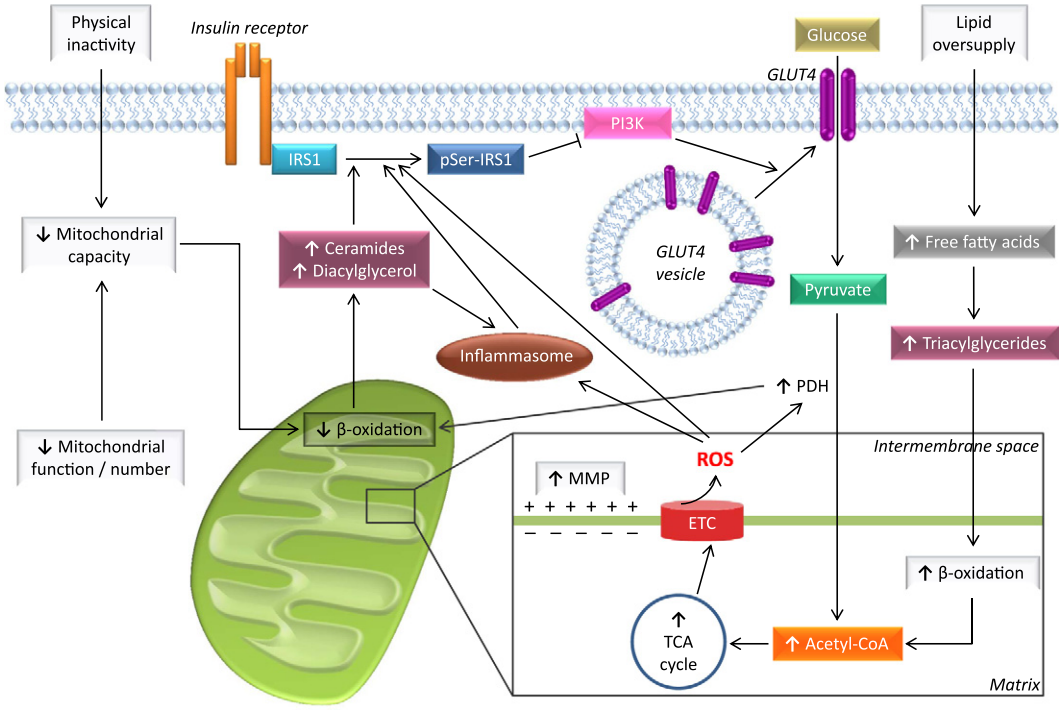

Fig. 1. Proposed mechanisms by which impaired mitochondrial function inhibits insulin action. Physical inactivity or intrinsic impairments in mitochondrial function and/or number reduce oxidative capacity, leading to reduced β-oxidation and accumulation of lipid species such as diacylglycerides and ceramides, which can ultimately impair the canonical insulin signalling pathway and GLUT4 translocation to the plasma membrane in skeletal muscle, adipose and the heart that results in insulin resistance. Alternatively, lipid oversupply increases β-oxidation that leads to hyper-reduction of the electron transport chain, increased mitochondrial membrane potential (MMP) and electron leak in the form of reactive oxygen species (ROS). Elevated ROS levels can impair insulin signalling either directly through as yet unresolved mechanisms, or through inflammasome activation. Elevated ROS levels also increase PDH activity that will lead to decreased β-oxidation and accumulation of intracellular lipids, which can also activate the inflammasome to induce insulin resistance.

insulin resistant *ob/ob* mice enhanced glucose and insulin tolerance [109]. However, cellular redox regulation is compartmentalised and mitochondrial ROS production is known to be regulated differently to that by plasma membrane bound oxidases for example. These initial discoveries did not specify the exact source of ROS that induced insulin resistance, but subsequent studies have focussed on the role of mitochondria in this response. Indeed, it has been observed that the mitochondria of obese and insulin resistant rodents and humans release greater ROS when compared with lean counterparts [110]. This has been hypothesised to be due to increased substrate delivery to the mitochondria under states of nutrient oversupply, which in turn results in hyper-reduction of the electron transport chain when there is subsequent increase in ATP demand. The resulting increase in mitochondrial membrane potential contributes to the leak of electrons from the electron transport chain, in the form of ROS [111]. These studies have been supported by studies using mitochondrial specific anti-oxidants, which ameliorate skeletal muscle insulin resistance induced by high fat feeding [110]. However, opposing findings on this approach have also been reported [112]. Subsequent studies have proposed that mitochondrial ROS production is a unifying mechanism describing a number of different forms of insulin resistance, including insulin resistance due to inflammation, hyperinsulinaemia and glucocorticoids, in addition to nutrient oversupply [113]. Furthermore, these findings were replicated in both myotubes and adipocytes [113]. The signalling events that these diverse insults engage to increase mitochondrial ROS production are not completely understood. It is known that inflammatory cytokines such as tumour necrosis factor α (TNFα) increase cytosolic ROS production through activation of NADPH oxidase (Nox) isoforms [114]. As the kinetics of cytosolic TNFα-induced ROS production precedes that of mitochondrial TNFα-induced ROS production, it has been proposed that oxidative damage to mitochondria from Nox-derived ROS is the driver of the TNFα-induced mitochondrial ROS response [115]. More recently, the synthetic glucocorticoid dexamethasone has been shown to directly inhibit complexes II and III of the electron transport chain, which is associated with increased mitochondrial ROS production [116]. The mechanism of insulin-induced mitochondrial ROS production remains elusive.

The exact mechanism by which mitochondrial ROS impairs insulin action is also not yet resolved. It has been proposed that an overall alteration in the cellular redox state towards oxidation could reduce global serine/threonine phosphatase activity, which would result in greater activity of the serine/threonine stress kinases that are thought to inhibit the canonical insulin signalling pathway, thereby reducing insulin action [111]. However, it has also been noted with experimental evidence that ROS is required for insulin sensitivity through the oxidation and inactivation of the protein tyrosine phosphatase (PTP) member phosphatase and tensin homolog (PTEN), which inactivates components of the insulin signalling pathway [117]. Alternative theories have also been posited, including the idea that oxidation of mitochondrial protein thiols enhances pyruvate dehydrogenase activity, which increases generation of acetyl-CoA from pyruvate for entry into the TCA cycle whilst simultaneously inactivating enzymes of β-oxidation, ultimately leading to ectopic lipid accumulation and impairments in insulin signalling [118,119]. Whilst experimental evidence is only just beginning to emerge to support this theory, it is consistent with much of the metabolic remodelling seen in insulin resistant states in humans.

4.3. Inflammation

As noted previously, chronic low grade inflammation is associated with insulin resistance. In a number of models across multiple species, insulin resistance is associated with macrophage accumulation in adipose tissue and tissue inflammatory responses in the liver and hypothalamus [120]. Similar to mitochondria, the role of inflammation in the development of insulin resistance is controversial, with some insulin resistant states being independent of any inflammatory response [121]. However, it is known that mitochondria can activate the inflammasome (Fig. 1), which is a multiprotein complex that initiates

and controls inflammatory reactions in response to stress insults, including oxidative stress [122]. Mitochondrial ROS is sufficient for inflammasome activation via the thioredoxin-interacting protein (TXNIP), which in turn activates a host of inflammatory signalling pathways and gene expression responses [123]. Many of the signalling pathways activated by the inflammatory response are serine/threonine kinases that can impair canonical insulin signalling, such as the c-Jun N-terminal kinase (JNK; [124]). Furthermore, release of mitochondrial DNA is sufficient for inflammasome activation, providing another link between mitochondria and the inflammatory response [125]. Inflammasome activation can also occur in response to elevation in lipids such as ceramides [126]. As increases in ceramides have been associated with impaired mitochondrial function [127], this provides yet another link between mitochondrial regulation of inflammation and provides a potential mechanistic link between ceramides and the development of insulin resistance. The exact role of mitochondrial control of inflammation in the aetiology of insulin resistance remains to be mechanistically established, however this provides another potential mechanism by which altered mitochondrial function could impact on insulin action.

5. Speculative mechanisms potentially linking mitochondria and insulin action

Despite many years of intensive research, the previous sections highlight that controversies still exist regarding the involvement of mitochondrial dysfunction in the development of insulin resistance. A clear contributor to this controversy is deficiencies in our understanding of aspects of mitochondrial biology in the context of insulin action. For example, a common assumption in this debate is that all deficiencies in mitochondrial function equate to a homogenous, unified response on insulin action. An obvious exception to this assumption is the mild inhibition of complex I by some anti-diabetic drugs, such as the biguanide [128] and thiazolidinedione [129] families of compounds. The biguanide metformin is the most widely prescribed anti-diabetic agent and is the first line of treatment for patients with insulin resistance [130]. This compound primarily exerts its effects in the liver and is associated with enhanced insulin suppression of glucose production [131]. It is thought that complex I inhibition by these drugs is sufficient to result in reduced hepatocyte energy status, whilst at the same time sparing substrate oxidation through complex II. The reduction in energy status activates the AMP-activated protein kinase (AMPK), which exerts a number of anti-diabetic actions [132], including the transcriptional downregulation of key gluconeogenic enzymes [133]. Alternatively, the reduction in energy status and associated increase in ADP and AMP nucleotides could allosterically regulate gluconeogenic enzyme activity directly [134]. Although the exact mechanism of action of these drugs continues to be debated [135], these data suggest that impairments in complex I function might not have detrimental effects on insulin action. One would predict that impairments in the function of other complexes of the electron transport chain might result in more detrimental effects on insulin action (Fig. 2). As the efficacy of these drugs is also largely restricted to the liver, this could suggest that tissue or cell type specific differences exist in how mitochondria impacts insulin action. Indeed, an aspect not widely considered when investigating the role of mitochondria and insulin action is the specific metabolic role of the tissue being examined and potential metabolite feedback responses that mitochondrial dysfunction would impart. Again, the metabolite signature might be specific for the site of mitochondrial impairment and the tissue in which it occurs.

Although mitochondrial ROS production has received the most attention as a putative retrograde signal linking mitochondrial dysfunction with insulin resistance, a host of other known mitochondrial retrograde signals have yet to be mechanistically studied in this context.

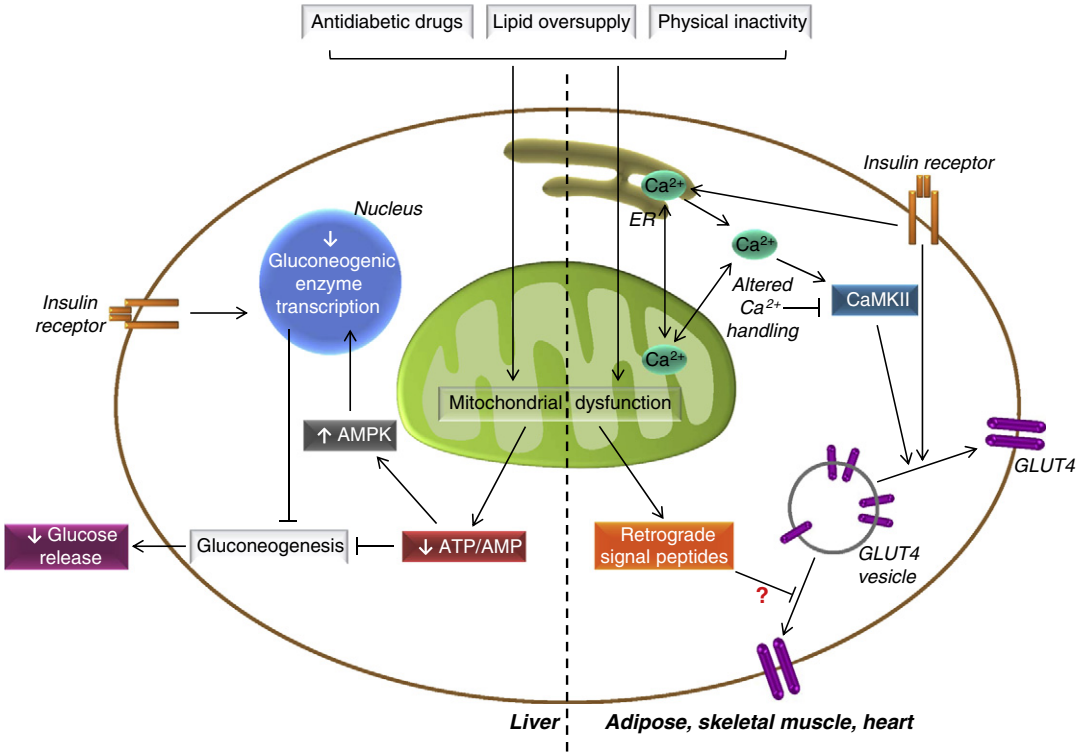

Fig. 2. Speculative mechanisms by which impaired mitochondrial function regulates insulin action. In adipose tissue, skeletal muscle and the heart, lipid oversupply, physical inactivity or intrinsic impairments in mitochondrial function and/or number could alter Ca^{2+} handling and insulin activation of CaMKII, reducing GLUT4 translocation and inducing insulin resistance. In addition, other mitochondrial retrograde signalling, such as mitochondrial stress protein release into the cytoplasm, could have similar effects. In the liver, acute mitochondrial dysfunction, such as that induced by anti-diabetic agents, could enhance insulin action through alterations in cellular energy balance that has allosteric inhibitory effects on insulin-regulated gluconeogenic enzymes. Alternatively, altered cellular energy balance that inhibits gluconeogenic gene expression via the AMP-activated protein kinase (AMPK) could also enhance hepatic insulin action.

These include Ca^{2+}, Fe^{2+}, nitric oxide and carbon monoxide, in addition to peptides released by mitochondria [37; Fig. 2]. For example, insulin-stimulated translocation of GLUT4 to the plasma membrane in adipocytes is dependent on calcium/calmodulin kinase II (CaMKII) phosphorylation of myosin-1c (Myo1c), a motor protein component of the cytoskeleton [136]. CaMKII activation is typically sensitive to increases in cellular Ca^{2+} concentration and whilst not specifically assessed in the context of insulin action, mitochondrial dysfunction that alters the Ca^{2+} buffering capacity of mitochondria could alter insulin-stimulated CaMKII activity and glucose transport (Fig. 2), the key measure of insulin action in these cells. Alterations in mitochondrial calcium handling have also been linked to the induction of ER stress and insulin resistance in the liver [137].

In addition, peptides released by the mitochondria under conditions of cellular stress could impact on insulin action (Fig. 2). Deletion of AIF from both the liver and muscle protects against the development of insulin resistance in response to high fat feeding [78]. As its name suggests, AIF was first characterised as a peptide that induces chromatin condensation and DNA fragmentation after its release from mitochondria in response to apoptosis signals [138]. However, AIF also forms part of complex I of the electron transport chain and therefore plays a role in oxidative phosphorylation and cell redox regulation. Deletion of AIF in mice reduced respiration in both muscle and liver and protected both tissues against insulin resistance. In addition, no differences were detected in the oxidative stress response in wild type and AIF knockout mice when fed a high fat diet [78]. It could be that the effects of AIF knockout on insulin action are mediated through similar elusive mechanisms to anti-diabetic agents that inhibit complex I. However, it could also be possible that AIF has unappreciated signalling roles that impact on cellular insulin action. Indeed, the idea that mitochondrial derived peptide release is critical for an integrated cellular response to stress is beginning to gain wider acceptance [37]. Further studies will be required to characterise the mitochondrial peptide signalling response to insults that induce insulin resistance in multiple cell and tissue types.

6. Summary

This review provides an overview of the hotly debated role of mitochondria in the development of insulin resistance and type 2 diabetes. Whilst there is no doubt of an association between impaired mitochondrial function and insulin resistance, the causality of this relationship remains controversial. This controversy is fuelled by our lack of understanding of some of the biological interactions between mitochondria and insulin regulated processes in the context of insults thought to induce insulin resistance. Furthermore, aspects that have not yet been considered are tissue/cell type specific responses, mitochondrial responses to site-specific impairments in mitochondrial function and as yet uncharacterised retrograde signalling from mitochondria. The complexity of mitochondria and the heterogeneous nature of insulin resistance will likely mean that unifying all-encompassing theories to describe the relationship between mitochondria and insulin action is not possible. Furthermore, arguments on this issue should not focus on whether impairments in mitochondrial function are universally required for the development of insulin resistance, but whether diverse and unique impairments in mitochondrial function are sufficient to contribute to insulin resistance.

Acknowledgements

We apologise to those authors whose work we could not cite due to space constraints. The Metabolic Remodelling Laboratory is supported by Project Grants (APP1027227 and APP1027227) from the NHMRC, the Diabetes Australia Research Trust, the Central Research Grant Scheme of Deakin University and the Deakin University Molecular and Medical Research Strategic Research Centre. SLM is also supported by a Career Development Fellowship from the NHMRC (1030474).

References

[1] P. Zimmet, K.G.M.M. Alberti, J. Shaw, Global and societal implications of the diabetes epidemic, Nature 414 (2000) 782–787.
[2] G. Danaei, M.M. Finucane, Y. Lu, G.M. Singh, M.J. Cowan, C.J. Paciorek, J.K. Lin, F. Farzadfar, Y.H. Khang, G.A. Stevens, M. Rao, M.K. Ali, L.M. Riley, C.A. Robinson, M. Ezzati, National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants, Lancet 378 (2011) 31–40.
[3] G. Roglic, N. Unwin, Mortality attributable to diabetes: estimates for the year 2010, Diabetes Res. Clin. Pract. 87 (2010) 15–19.
[4] M. Ezzati, A.B. Friedman, S.C. Kulkarni, C.J. Murray, The reversal of fortunes: trends in county mortality and cross-county mortality disparities in the United States, PLoS Med. 22 (2008) e66.
[5] World Health Organisation, Preventing Chronic Diseases, a Vital Investment, WHO Global Report, WHO, 2005.
[6] V.T. Samuel, K.F. Petersen, G.I. Shulman, Lipid-induced insulin resistance: unravelling the mechanism, Lancet 375 (2010) 2267–2277.
[7] B.H. Goodpaster, Mitochondrial deficiency is associated with insulin resistance, Diabetes 62 (2013) 1032–1035.
[8] J.O. Holloszy, "Deficiency" of mitochondria in muscle does not cause insulin resistance, Diabetes 62 (2013) 1036–1040.
[9] B. Cheatham, C.R. Kahn, Insulin action and the insulin signalling network, Endocr. Rev. 16 (1995) 117–142.
[10] C.M. Taniguchi, B. Emanuelli, C.R. Kahn, Critical nodes in signalling pathways: insights into insulin action, Nat. Rev. Mol. Cell Biol. 7 (2006) 85–96.
[11] L. Varela, T.L. Horvath, Leptin and insulin pathways in POMC and AgRP neurons that modulate energy balance and glucose homeostasis, EMBO Rep. 13 (2012) 1079–1086.
[12] Z.R. Zierath, L. He, A. Gumà, E. Odegoard Wahlström, A. Klip, H. Wallberg-Henriksson, Insulin action on glucose transport and plasma membrane GLUT4 content in skeletal muscle from patients with NIDDM, Diabetologia 39 (1996) 1180–1189.
[13] N.J. Bryant, R. Govers, D.E. James, Regulated transport of the glucose transporter GLUT4, Nat. Rev. Mol. Cell Biol. 3 (2002) 267–277.
[14] D. Thiebaud, E. Jacot, R.A. DeFronzo, E. Maeder, E. Jequier, J.P. Felber, The effect of graded doses of insulin on total glucose uptake, glucose oxidation, and glucose storage in man, Diabetes 31 (1982) 957–963.
[15] P.D. Hone, G. Pacini, Hepatic dysfunction and insulin insensitivity in type 2 diabetes mellitus: a critical target for insulin-sensitizing agents, Diabetes Obes. Metab. 10 (2008) 699–718.
[16] M.D. Michael, R.N. Kulkarni, C. Postic, S.F. Previs, G.I. Shulman, M.A. Magnuson, C.R. Kahn, Loss of insulin signaling in hepatocytes leads to severe insulin resistance and progressive hepatic dysfunction, Mol. Cell 6 (2000) 87–97.
[17] G. Boden, Obesity, insulin resistance and free fatty acids, Curr. Opin. Endocrinol. Diabetes Obes. 18 (2011) 139–143.
[18] T. Suganami, M. Tanaka, Y. Ogawa, Adipose tissue inflammation and ectopic lipid accumulation, Endocr. J. 59 (2012) 849–857.
[19] C.H. Mandavia, A.R. Aroor, V.G. Demarco, J.R. Sowers, Molecular and metabolic mechanisms of cardiac dysfunction in diabetes, Life Sci. 92 (2013) 601–608.
[20] J.S. Marino, Y. Xu, J.W. Hill, Central insulin and leptin-mediated autonomic control of glucose homeostasis, Trends Endocrinol. Metab. 22 (2011) 275–285.
[21] M. Brownlee, Banting Lecture 2004: the pathobiology of diabetic complications — a unifying mechanism, Diabetes 54 (2005) 1615.
[22] M. Murea, L. Ma, B.I. Freedman, Genetic and environmental factors associated with type 2 diabetes and diabetic vascular complications, Rev. Diabet. Stud. 9 (2012) 6–22.
[23] V.T. Samuel, G.I. Shulman, Mechanisms for insulin resistance: common threads and missing links, Cell 148 (2012) 852–871.
[24] D.A. Harris, A.M. Das, Control of mitochondrial ATP synthesis in the heart, Biochem. J. 280 (1991) 561–573.
[25] D.R. Winge, Sealing the mitochondrial respirasome, Mol. Cell. Biol. 32 (2012) 2647–2652.
[26] M.D. Stobbe, S.M. Houten, A.H. van Kampen, R.J. Wanders, P.D. Moerland, Improving the description of metabolic networks: the TCA cycle as example, FASEB J. 26 (2012) 3625–3636.
[27] S. Papa, P.L. Martino, G. Capitanio, A. Gaballo, D. De Rasmo, A. Signorile, V. Petruzzella, The oxidative phosphorylation system in mammalian mitochondria, Adv. Exp. Med. Biol. 942 (2012) 3–37.
[28] M.D. Brand, D.G. Nicholls, Assessing mitochondrial dysfunction in cells, Biochem. J. 435 (2011) 297–312.
[29] D.F. Rolfe, M.D. Brand, Contribution of mitochondrial proton leak to skeletal muscle respiration and to standard metabolic rate, Am. J. Physiol. Cell Physiol. 271 (1996) C1380–C1389.
[30] A. Boveris, J.J. Poderoso, M.C. Carreras, E. Cadenas, Regulation of mitochondrial respiration by oxygen and nitric oxide, Ann. N. Y. Acad. Sci. 899 (2000) 121–135.
[31] S. Dröse, U. Brandt, Molecular mechanisms of superoxide production by the mitochondrial respiratory chain, Adv. Exp. Med. Biol. 748 (2012) 145–169.
[32] L. Galluzzi, O. Kepp, G. Kroemer, Mitochondria: master regulators of danger signalling, Nat. Rev. Mol. Cell Biol. 13 (2012) 780–788.
[33] J.C. Rathmell, C.B. Thompson, Pathways of apoptosis in lymphocyte development, homeostasis and disease, Cell 109 (2002) S97–S107.

[34] J.C. Reed, Mechanisms of apoptosis, Am. J. Pathol. 157 (2000) 1415–1430.
[35] D. Wallach, T.B. Kang, A. Kovalenko, The extrinsic cell death pathway and the élan mortel, Cell Death Differ. 15 (2008) 1533–1541.
[36] M.P. Murphy, How mitochondria produce reactive oxygen species, Biochem. J. 417 (2009) 1–13.
[37] C. Lee, K. Yen, P. Cohen, Humanin: a harbinger of mitochondrial derived peptides? Trends Endocrinol. Metab. 24 (2013) 222–228.
[38] I. Drago, P. Pizzo, T. Pozzan, After half a century mitochondrial calcium in- and efflux machineries reveal themselves, EMBO J. 30 (2011) 4119–4125.
[39] A.I. Tarasov, E.J. Griffiths, G.A. Rutter, Regulation of ATP production by mitochondrial Ca^{2+}, Cell Calcium 52 (2012) 28–35.
[40] B. Glancy, R.S. Balaban, Protein composition and function of red and white skeletal muscle mitochondria, Am. J. Physiol. Cell Physiol. 300 (2011) C1280–C1290.
[41] S. Pan, S.Y. Ryu, S.S. Sheu, Distinctive characteristics and functions of multiple mitochondrial Ca^{2+} influx mechanisms, Sci. China Life Sci. 54 (2011) 763–769.
[42] K. Mallilankaraman, P. Doonan, C. Cárdenas, H.C. Chandramoorthy, M. Müller, R. Miller, N.E. Hoffman, R.K. Gandhirajan, J. Molgó, M.J. Birnbaum, B.S. Rothberg, D.O. Mak, J.K. Foskett, M. Madesh, MICU1 is an essential gatekeeper for MCU-mediated mitochondrial Ca^{2+} uptake that regulates cell survival, Cell 151 (2012) 630–644.
[43] R. Palty, W.F. Silverman, M. Hershfinkel, T. Caporale, S.L. Sensi, J. Parnis, C. Nolte, D. Fishman, V. Shoshan-Barmatz, S. Herrmann, D. Khananshvili, I. Sekler, NCLX is an essential component of mitochondrial Na^+/Ca^{2+} exchange, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 436–441.
[44] R. Palty, I. Sekler, The mitochondrial Na^+/Ca^{2+} exchanger, Cell Calcium 52 (2012) 9–15.
[45] P. Bernardi, S. von Stockum, The permeability transition pore as a Ca(2+) release channel: new answers to an old question, Cell Calcium 52 (2012) 22–27.
[46] A. Rasola, P. Bernardi, Mitochondrial permeability transition in Ca(2+)-dependent apoptosis and necrosis, Cell Calcium 50 (2011) 222–233.
[47] W. Reardon, R.J. Ross, M.G. Sweeney, L.M. Luxon, M.E. Pembrey, A.E. Harding, R.C. Trembath, Diabetes mellitus associated with a pathogenic point mutation in mitochondrial DNA, Lancet 340 (1992) 1376–1379.
[48] T. Kadowaki, H. Kadowaki, Y. Mori, K. Tobe, R. Sakuta, Y. Suzuki, Y. Tanabe, H. Sakura, T. Awata, Y. Goto, A subtype of diabetes mellitus associated with a mutation of mitochondrial DNA, N. Engl. J. Med. 330 (1994) 962–968.
[49] R. Becker, H. Laube, T. Linn, M.S. Damian, Insulin resistance in patients with the mitochondrial tRNA(Leu(UUR)) gene mutation at position 3243, Exp. Clin. Endocrinol. Diabetes 110 (2002) 291–297.
[50] D.E. Kelley, M. Mokan, J.A. Simoneau, L.J. Mandarino, Interaction between glucose and free fatty acid metabolism in human skeletal muscle, J. Clin. Invest. 92 (1993) 91–98.
[51] D.E. Kelley, J.A. Simoneau, Impaired free fatty acid utilization by skeletal muscle in non-insulin-dependent diabetes mellitus, J. Clin. Invest. 94 (1994) 2349–2356.
[52] J.A. Simoneau, D.E. Kelley, Altered glycolytic and oxidative capacities of skeletal muscle contribute to insulin resistance in NIDDM, J. Appl. Physiol. 83 (1997) 166–171.
[53] D.E. Kelley, J. He, E.V. Menshikova, V.B. Ritov, Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes, Diabetes 51 (2002) 2944–2950.
[54] R. Boushel, E. Gnaiger, P. Schjerling, M. Skovbro, R. Kraunsøe, F. Dela, Patients with type 2 diabetes have normal mitochondrial function in skeletal muscle, Diabetologia 50 (2007) 790–796.
[55] V.B. Ritov, E.V. Menshikova, J. He, R.E. Ferrell, B.H. Goodpaster, D.E. Kelley, Deficiency of subsarcolemmal mitochondria in obesity and type 2 diabetes, Diabetes 54 (2005) 8–14.
[56] M. Mogensen, K. Sahlin, M. Fernström, D. Glintborg, B.F. Vind, H. Beck-Nielsen, K. Højlund, Mitochondrial respiration is decreased in skeletal muscle of patients with type 2 diabetes, Diabetes 56 (2007) 1592–1599.
[57] E. Phielix, V.B. Schrauwen-Hinderling, M. Mensink, E. Lenaers, R. Meex, J. Hoeks, M.E. Kooi, E. Moonen-Kornips, J.P. Sels, M.K. Hesselink, P. Schrauwen, Lower intrinsic ADP-stimulated mitochondrial respiration underlies in vivo mitochondrial dysfunction in muscle of male type 2 diabetic patients, Diabetes 57 (2008) 2943–2949.
[58] X. Huang, K.F. Eriksson, A. Vaag, M. Lehtovirta, M. Hansson, E. Laurila, T. Kanninen, B.T. Olesen, I. Kurucz, L. Koranyi, L. Groop, Insulin-regulated mitochondrial gene expression is associated with glucose flux in human skeletal muscle, Diabetes 48 (1999) 1508–1514.
[59] L. Mustelin, K.H. Pietiläinen, A. Rissanen, A.R. Sovijärvi, P. Piirilä, J. Naukkarinen, L. Peltonen, J. Kaprio, H. Yki-Järvinen, Acquired obesity and poor physical fitness impair expression of genes of mitochondrial oxidative phosphorylation in monozygotic twins discordant for obesity, Am. J. Physiol. Endocrinol. Metab. 295 (2008) E148–E154.
[60] T. Rönn, P. Poulsen, T. Tuomi, B. Isomaa, L. Groop, A. Vaag, C. Ling, Genetic variation in ATP5O is associated with skeletal muscle ATP50 mRNA expression and glucose uptake in young twins, PLoS One 4 (2009) e4793.
[61] V. Rimbert, Y. Boirie, M. Bedu, J.F. Hocquette, P. Ritz, B. Morio, Muscle fat oxidative capacity is not impaired by age but by physical inactivity: association with insulin sensitivity, FASEB J. 18 (2004) 737–739.
[62] F.H. van Tienen, S.F. Praet, H.M. de Feyter, N.M. van den Broek, P.J. Lindsey, K.G. Schoonderwoerd, I.F. de Coo, K. Nicolay, J.J. Prompers, H.J. Smeets, L.J. van Loon, Physical activity is the key determinant of skeletal muscle mitochondrial function in type 2 diabetes, J. Clin. Endocrinol. Metab. 97 (2012) 3261–3269.
[63] K.F. Petersen, S. Dufour, D. Befroy, R. Garcia, G.I. Shulman, Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes, N. Engl. J. Med. 350 (2004) 664–671.
[64] M.E. Patti, A.J. Butte, S. Crunkhorn, K. Cusi, R. Berria, S. Kashyap, Y. Miyazaki, I. Kohane, M. Costello, R. Saccone, E.J. Landaker, A.B. Goldfine, E. Mun, R. DeFronzo, J. Finlayson, C.R. Kahn, L.J. Mandarino, Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 8466–8471.
[65] V.K. Mootha, C.M. Lindgren, K.F. Eriksson, A. Subramanian, S. Sihag, J. Lehar, P. Puigserver, E. Carlsson, M. Ridderstråle, E. Laurila, N. Houstis, M.J. Daly, N. Patterson, J.P. Mesirov, T.R. Golub, P. Tamayo, B. Spiegelman, E.S. Lander, J.N. Hirschhorn, D. Altshuler, L.C. Groop, PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes, Nat. Genet. 34 (2003) 267–273.
[66] K. Baar, A.R. Wende, T.E. Jones, M. Marison, L.A. Nolte, M. Chen, D.P. Kelly, J.O. Holloszy, Adaptations of skeletal muscle to exercise: rapid increase in the transcriptional coactivator PGC-1, FASEB J. 14 (2002) 1879–1886.
[67] K. Morino, K.F. Petersen, G.I. Shulman, Molecular mechanisms of insulin resistance in humans and their potential links with mitochondrial dysfunction, Diabetes 55 (2006) S9–S15.
[68] H.K. Karlsson, M. Ahlsén, J.R. Zierath, H. Wallberg-Henriksson, H.A. Koistinen, Insulin signaling and glucose transport in skeletal muscle from first-degree relatives of type 2 diabetic patients, Diabetes 55 (2006) 1283–1288.
[69] C.S. Choi, D.E. Befroy, R. Codella, S. Kim, R.M. Reznick, Y.J. Hwang, Z.X. Liu, H.Y. Lee, A. Distefano, V.T. Samuel, D. Zhang, G.W. Cline, C. Handschin, J. Lin, K.F. Petersen, B.M. Spiegelman, G.I. Shulman, Paradoxical effects of increased expression of PGC-1alpha on muscle mitochondrial function and insulin-stimulated muscle glucose metabolism, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 19926–19931.
[70] K.F. Petersen, D. Befroy, S. Dufour, J. Dziura, C. Ariyan, D.L. Rothman, L. DiPietro, G.W. Cline, G.I. Shulman, Mitochondrial dysfunction in the elderly: possible role in insulin resistance, Science 300 (2003) 1140–1142.
[71] P. Chomentowski, P.M. Coen, Z. Radikova, B.H. Goodpaster, F.G. Toledo, Skeletal muscle mitochondria in insulin resistance: differences in intermyofibrillar versus subsarcolemmal subpopulations and relationship to metabolic flexibility, J. Clin. Endocrinol. Metab. 96 (2011) 494–503.
[72] R. Fabris, G. Mingrone, G. Milan, M. Manco, M. Granzotto, A.D. Pozza, A. Scarda, R. Serra, A.V. Greco, G. Federspil, R. Vettor, Further lowering of muscle lipid oxidative capacity in obese subjects after bilopancreatic diversion, J. Clin. Endocrinol. Metab. 89 (2004) 1753–1759.
[73] J.R. Berggren, K.E. Boyle, W.H. Chapman, J.A. Houmard, Skeletal muscle lipid oxidation and obesity: influence of weight loss and exercise, Am. J. Physiol. Endocrinol. Metab. 294 (2008) E726–E732.
[74] F.G. Toledo, E.V. Menshikova, K. Azuma, Z. Radikova, C.A. Kelley, V.B. Ritov, D.E. Kelley, Mitochondrial capacity in skeletal muscle is not stimulated by weight loss despite increases in insulin action and decreases in intramyocellular lipid content, Diabetes 57 (2008) 987–994.
[75] C. Bonnard, A. Durand, S. Peyrol, E. Chanseaume, M.A. Chauvin, B. Morio, H. Vidal, J. Rieusset, Mitochondrial dysfunction results from oxidative stress in the skeletal muscle of diet-induced insulin-resistant mice, J. Clin. Invest. 118 (2008) 789–800.
[76] N. Turner, C.R. Bruce, S.M. Beale, K.L. Hoehn, T. So, M.S. Rolph, G.J. Cooney, Excess lipid availability increases mitochondrial fatty acid oxidative capacity in muscle: evidence against a role for reduced fatty acid oxidation in lipid-induced insulin resistance in rodents, Diabetes 56 (2007) 2085–2092.
[77] J.A. Simoneau, J.H. Veerkamp, L.P. Turcotte, D.E. Kelley, Markers of capacity to utilize fatty acids in human skeletal muscle: relation to insulin resistance and obesity and effects of weight loss, FASEB J. 13 (1999) 2051–2060.
[78] J.A. Pospisilik, C. Knauf, N. Joza, P. Benit, M. Orthofer, P.D. Cani, I. Ebersberger, T. Nakashima, R. Sarao, G. Neely, H. Esterbauer, A. Kozlov, C.R. Kahn, G. Kroemer, P. Rustin, R. Burcelin, J.M. Penninger, Targeted deletion of AIF decreases mitochondrial oxidative phosphorylation and protects from obesity and diabetes, Cell 2007 (131) (2007) 476–491.
[79] R. Quintens, S. Singh, K. Lemaire, K. De Bock, M. Granvik, A. Schraenen, I.O. Vroegrijk, V. Costa, P. Van Noten, D. Lambrechts, S. Lehnert, L. Van Lommel, L. Thorrez, G. De Faudeur, J.A. Romijn, J.M. Shelton, L. Scorrano, H.R. Lijnen, P.J. Voshol, P. Carmeliet, P.P. Mammen, F. Schuit, Mice deficient in the respiratory chain gene Cox6a2 are protected against high-fat diet-induced obesity and insulin resistance, PLoS One 8 (2013) e56719.
[80] D.H. Han, C.R. Hancock, S.R. Jung, K. Higashida, S.H. Kim, J.O. Holloszy, Deficiency of the mitochondrial electron transport chain in muscle does not cause insulin resistance, PLoS One 12 (2011) e19739.
[81] A. Wredenberg, C. Freyer, M.E. Sandström, A. Katz, R. Wibom, H. Westerblad, N.G. Larsson, Respiratory chain dysfunction in skeletal muscle does not cause insulin resistance, Biochem. Biophys. Res. Commun. 350 (2006) 202–207.
[82] C. Zechner, L. Lai, J.F. Zechner, T. Geng, Z. Yan, J.W. Rumsey, D. Collia, Z. Chen, D.F. Wozniak, T.C. Leone, D.P. Kelly, Total skeletal muscle PGC-1 deficiency uncouples mitochondrial derangements from fiber type determination and insulin sensitivity, Cell Metab. 12 (2010) 633–642.
[83] S.R. Preis, J.M. Massaro, S.J. Robins, U. Hoffmann, R.S. Vasan, T. Irlbeck, J.B. Meigs, P. Sutherland, R.B. D'Agostino Sr., C.J. O'Donnell, C.S. Fox, Abdominal subcutaneous and visceral adipose tissue and insulin resistance in the Framingham heart study, Obesity 18 (2010) 2191–2198.
[84] P. Mitrou, E. Boutati, V. Lambadiari, E. Maratou, A. Papakonstantinou, V. Komesidou, L. Sidossis, N. Tountas, N. Katsilambros, T. Economopoulos, S.A. Raptis, G. Dimitriadis, Rates of glucose uptake in adipose tissue and muscle *in vivo* after a mixed meal in women with morbid obesity, J. Clin. Endocrinol. Metab. 94 (2009) 2958–2961.
[85] L. Wilson-Fritch, S. Nicoloro, M. Chouinard, M.A. Lazar, P.C. Chui, J. Leszyk, J. Straubhaar, M.P. Czech, S. Corvera, Mitochondrial remodeling in adipose tissue associated with obesity and treatment with rosiglitazone, J. Clin. Invest. 114 (2004) 1281–1289.
[86] H.J. Choo, J.H. Kim, O.B. Kwon, C.S. Lee, J.Y. Mun, S.S. Han, Y.S. Yoon, G. Yoon, K.M. Choi, Y.G. Ko, Mitochondria are impaired in the adipocytes of type 2 diabetic mice, Diabetologia 49 (2006) 784–791.

[87] J.X. Rong, Y. Qiu, M.K. Hansen, L. Zhu, V. Zhang, M. Xie, Y. Okamoto, M.D. Mattie, H. Higashiyama, S. Asano, J.C. Strum, T.E. Ryan, Adipose mitochondrial biogenesis is suppressed in db/db and high-fat diet-fed mice and improved by rosiglitazone, Diabetes 56 (2007) 1751–1760.
[88] I. Bogacka, H. Xie, G.A. Bray, S.R. Smith, Pioglitazone induces mitochondrial biogenesis in human subcutaneous adipose tissue in vivo, Diabetes 54 (2005) 1392–1399.
[89] M.J. Laye, R.S. Rector, S.O. Warner, S.P. Naples, A.L. Perretta, G.M. Uptergrove, M.H. Laughlin, J.P. Thyfault, F.W. Booth, J.A. Ibdah, Changes in visceral adipose tissue mitochondrial content with type 2 diabetes and daily voluntary wheel running in OLETF rats, J. Physiol. 587 (2009) 3729–3739.
[90] L.N. Sutherland, L.C. Capozzi, N.J. Turchinsky, R.C. Bell, D.C. Wright, Time course of high-fat diet-induced reductions in adipose tissue mitochondrial proteins: potential mechanisms and the relationship to glucose intolerance, Am. J. Physiol. Endocrinol. Metab. 295 (2008) E1076–E1083.
[91] J. Szendroedi, M. Chmelik, A.I. Schmid, P. Nowotny, A. Brehm, M. Krssak, E. Moser, M. Roden, Abnormal hepatic energy homeostasis in type 2 diabetes, Hepatology 50 (2009) 1079–1086.
[92] A.I. Schmid, J. Szendroedi, M. Chmelik, M. Krssák, E. Moser, M. Roden, Liver ATP synthesis is lower and relates to insulin sensitivity in patients with type 2 diabetes, Diabetes Care 34 (2011) 448–453.
[93] S. Bouderba, M.N. Sanz, C. Sánchez-Martín, M.Y. El-Mir, G.R. Villanueva, D. Detaille, E.A. Koceïr, Hepatic mitochondrial alterations and increased oxidative stress in nutritional diabetes-prone *Psammomys obesus* model, Exp. Diabetes Res. 2012 (2012) 430176.
[94] T.H. Kuo, K.H. Moore, F. Giacomelli, J. Wiener, Defective oxidative metabolism of heart mitochondria from genetically diabetic mice, Diabetes 32 (1983) 781–787.
[95] T.H. Kuo, F. Giacomelli, J. Wiener, K. Lapanowski-Netzel, Pyruvate dehydrogenase activity in cardiac mitochondria from genetically diabetic mice, Diabetes 34 (1995) 1075–1081.
[96] S. Boudina, S. Sena, B.T. O'Neill, P. Tathireddy, M.E. Young, E.D. Abel, Reduced mitochondrial oxidative capacity and increased mitochondrial uncoupling impair myocardial energetics in obesity, Circulation 112 (2005) 2686–2695.
[97] J. Buchanan, P.K. Mazumder, P. Hu, G. Chakrabarti, M.W. Roberts, U.J. Yun, R.C. Cooksey, S.E. Litwin, E.D. Abel, Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity, Endocrinology 146 (2005) 5341–5349.
[98] O.J. How, E. Aasum, D.L. Severson, W.Y. Chan, M.F. Essop, T.S. Larsen, Increased myocardial oxygen consumption reduces cardiac efficiency in diabetic mice, Diabetes 55 (2006) 466–473.
[99] S. Boudina, S. Sena, H. Theobald, X. Sheng, J.J. Wright, X.X. Hu, S. Aziz, J.J. Johnson, H. Bugger, V.G. Zaha, E.D. Abel, Mitochondrial energetics in the heart in obesity-related diabetes: direct evidence for increased uncoupled respiration and activation of uncoupling protein, Diabetes 32 (2007) 781–787.
[100] S. Boudina, H. Bugger, S. Sena, B.T. O'Neill, V.G. Zaha, O. Ilkun, J.J. Wright, P.K. Mazumder, E. Palfreyman, T.J. Tidwell, H. Theobald, O. Khalimonchuk, B. Wayment, X. Sheng, K.J. Rodnick, R. Centini, D. Chen, S.E. Litwin, B.E. Weimer, E.D. Abel, Contribution of impaired myocardial insulin signaling to mitochondrial dysfunction and oxidative stress in the heart, Circulation 119 (2009) 1272–1283.
[101] G. Ye, N.S. Metreveli, J. Ren, P.N. Epstein, Metallothionein prevents diabetes-induced deficits in cardiomyocytes by inhibiting reactive oxygen species production, Diabetes 52 (2003) 777–783.
[102] S. Gray, J.K. Kim, New insights into insulin resistance in the diabetic heart, Trends Endocrinol. Metab. 22 (2011) 394–403.
[103] B.B. Lowell, G.I. Shulman, Mitochondrial dysfunction and type 2 diabetes, Science 307 (2005) 384–387.
[104] K. Morino, K.F. Petersen, S. Dufour, D. Befroy, J. Frattini, N. Shatzkes, S. Neschen, M.F. White, S. Bilz, S. Sono, M. Pypaert, G.I. Shulman, Reduced mitochondrial density and increased IRS-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents, J. Clin. Invest. 115 (2005) 3587–3593.
[105] C.R. Bruce, A.J. Hoy, N. Turner, M.J. Watt, T.L. Allen, K. Carpenter, G.J. Cooney, M.A. Febbraio, E.W. Kraegen, Overexpression of carnitine palmitoyltransferase-1 in skeletal muscle is sufficient to enhance fatty acid oxidation and improve high-fat diet-induced insulin resistance, Diabetes 58 (2009) 550–558.
[106] E. Gnaiger, Capacity of oxidative phosphorylation in human skeletal muscle: new perspectives of mitochondrial physiology, Int. J. Biochem. Cell Biol. 41 (2009) 1837–1845.
[107] T.R. Koves, J.R. Ussher, R.C. Noland, D. Slentz, M. Mosedale, O. Ilkayeva, J. Bain, R. Stevens, J.R. Dyck, C.B. Newgard, G.D. Lopaschuk, D.M. Muoio, Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance, Cell Metab. 7 (2008) 45–56.
[108] K.L. Hoehn, C. Hohnen-Behrens, A. Cederberg, L.E. Wu, N. Turner, T. Yuasa, Y. Ebina, D.E. James, IRS1-independent defects define major nodes of insulin resistance, Cell Metab. 7 (2008) 421–433.
[109] N. Houstis, E.D. Rosen, E.S. Lander, Reactive oxygen species have a causal role in multiple forms of insulin resistance, Nature 440 (2006) 944–948.
[110] E.J. Anderson, M.E. Lustig, K.E. Boyle, T.L. Woodlief, D.A. Kane, C.T. Lin, J.W. Price III, L. Kang, P.S. Rabinovitch, H.H. Szeto, J.A. Houmard, R.N. Cortright, D.H. Wasserman, P.D. Neufer, Mitochondrial H_2O_2 emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans, J. Clin. Invest. 119 (2009) 573–581.
[111] K.H. Fisher-Wellman, P.D. Neufer, Linking mitochondrial bioenergetics to insulin resistance via redox biology, Trends Endocrinol. Metab. 23 (2012) 142–153.
[112] S. Paglialunga, B. van Bree, M. Bosma, M.P. Valdecantos, E. Amengual-Cladera, J.A. Jörgensen, D. van Beurden, G.J. den Hartog, D.M. Ouwens, J.J. Briedé, P. Schrauwen, J. Hoeks, Targeting of mitochondrial reactive oxygen species production does not avert lipid-induced insulin resistance in muscle tissue from mice, Diabetologia 55 (2012) 2759–2768.
[113] K.L. Hoehn, A.B. Salmon, C. Hohnen-Behrens, N. Turner, A.J. Hoy, G.J. Maghzal, R. Stocker, H. Van Remmen, E.W. Kraegen, G.J. Cooney, A.R. Richardson, D.E. James, Insulin resistance is a cellular antioxidant defense mechanism, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 17787–17792.
[114] Q. Li, N.Y. Spencer, F.D. Oakley, G.R. Buettner, J.F. Engelhardt, Endosomal Nox2 facilitates redox-dependent induction of NF-kappaB by TNF-alpha, Antioxid. Redox Signal. 11 (2009) 1249–1263.
[115] M.J. Morgan, Z.G. Liu, Reactive oxygen species in TNFα-induced signalling and cell death, Mol. Cells 30 (2010) 1–12.
[116] M.E. Tome, K. Lee, M.C. Jaramillo, M.M. Briehl, Mitochondria are the primary source of the H(2)O(2) signal for glucocorticoid-induced apoptosis of lymphoma cells, Exp. Ther. Med. 4 (2) (Feb 2012) 237–242.
[117] K. Loh, H. Deng, A. Fukushima, X. Cai, B. Boivin, S. Galic, C.R. Bruce, B.J. Shields, B. Skiba, L.M. Ooms, N. Stepto, B. Wu, C.A. Mitchell, N.K. Tonks, M.J. Watt, M.A. Febbraio, P.J. Crack, S. Andrikopoulos, T. Tiganis, Reactive oxygen species enhance insulin sensitivity, Cell Metab. 10 (2009) 260–272.
[118] T.R. Hurd, Y. Collins, I. Abakumova, E.T. Chouchani, B. Baranowski, I.M. Fearnley, T.A. Prime, M.P. Murphy, A.M. James, Inactivation of pyruvate dehydrogenase kinase 2 by mitochondrial reactive oxygen species, J. Biol. Chem. 287 (2012) 35153–35160.
[119] A.M. James, Y. Collins, A. Logan, M.P. Murphy, Mitochondrial oxidative stress and the metabolic syndrome, Trends Endocrinol. Metab. 23 (2012) 429–434.
[120] A.M. Johnson, J.M. Olefsky, The origins and drivers of insulin resistance, Cell 152 (2013) 673–684.
[121] N. Turner, G.M. Kowalski, S.J. Leslie, S. Risis, C. Yang, R.S. Lee-Young, J.R. Babb, P.J. Meikle, G.I. Lancaster, D.C. Henstridge, P.J. White, E.W. Kraegen, A. Marette, G.J. Cooney, M.A. Febbraio, C.R. Bruce, Diabetologia 56 (2013) 1638–1648.
[122] R. Zhou, A.S. Yazdi, P. Menu, J. Tschopp, A role for mitochondria in NLRP3 inflammasome activation, Nature 469 (2011) 221–225.
[123] T. Lane, B. Flam, R. Lockey, N. Kolliputi, TXNIP shuttling: the missing link bet6ween oxidative stress and inflammasome activation, Front. Physiol. 4 (2013) 50.
[124] S.N. Vallerie, G.S. Hotamisligil, The role of JNK proteins in metabolism, Sci. Transl. Med. 2 (2010) 60vr5.
[125] K. Shimada, T.R. Crother, J. Karlin, J. Dagvadorj, N. Chiba, S. Chen, V.K. Ramanujan, A.J. Wolf, L. Vergnes, D.M. Ojcius, A. Rentsendorj, M. Vargas, C. Guerrero, Y. Wang, K.A. Fitzgerald, D.M. Underhill, T. Town, M. Arditi, Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis, Immunity 36 (2012) 401–414.
[126] B. Vandanmagsar, Y.H. Youm, A. Ravussin, J.E. Galgani, K. Stadler, R.L. Mynatt, E. Ravussin, J.M. Stephens, V.D. Dixit, The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance, Nat. Med. 17 (2011) 179–188.
[127] J. Yu, S.A. Novgorodov, D. Chudakova, H. Zhu, A. Bielawska, J. Bielawski, L.M. Obeid, M.S. Kindy, T.I. Gudz, JNK3 signaling pathway activates ceramide synthase leading to mitochondrial dysfunction, J. Biol. Chem. 282 (2007) 25940–25949.
[128] M.R. Owen, E. Doran, A.P. Halestrap, Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain, Biochem. J. 348 (2000) 607–614.
[129] B. Brunmair, K. Staniek, F. Gras, N. Schaf, A. Althaym, R. Clara, M. Roden, E. Gnaiger, H. Nohl, W. Waldhausl, C. Furnsinn, Thiazolidinediones, like metformin, inhibit respiratory complex I: a common mechanism contributing to their anti-diabetic actions? Diabetes 53 (2004) 1052–1059.
[130] N. Papanas, E. Maltezos, Metformin: a review of its use in the treatment of type 2 diabetes, Clin. Med. Ther. 1 (2009) 1367–1381.
[131] R.S. Hundal, M. Krssak, S. Dufour, D. Laurent, V. Lebon, V. Chandramouli, S.E. Inzucchi, W.C. Schumann, K.T. Petersen, B.R. Landau, G.I. Shulman, Mechanism by which metformin reduces glucose production in type 2 diabetes, Diabetes 49 (2000) 2063–2069.
[132] G. Zhou, R. Myers, Y. Li, Y. Chen, X. Shen, J. Fenyk-Melody, M. Wu, J. Ventre, T. Doebber, N. Fujii, N. Musi, M.F. Hirshman, L.J. Goodyear, D.E. Moller, Role of AMP-activated protein kinase in mechanism of metformin action, J. Clin. Invest. 108 (2001) 1167–1174.
[133] A. Hubert, A. Husson, A. Chédeville, A. Lavoinne, AMP-activated protein kinase counteracted the inhibitory effect of glucose on the phosphoenolpyruvate carboxykinase gene expression in rat hepatocytes, FEBS Lett. 481 (2000) 209–212.
[134] M. Foretz, S. Hébrard, J. Leclerc, E. Zarrinpashneh, M. Soty, G. Mithieux, K. Sakamoto, F. Andreelli, B. Viollet, Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state, J. Clin. Invest. 120 (2010) 2355–2369.
[135] R.A. Miller, Q. Chu, J. Xie, M. Foretz, B. Viollet, M.J. Birnbaum, Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP, Nature 494 (2013) 256–260.
[136] M.F. Yip, G. Ramm, M. Larance, K.L. Hoehn, M.C. Wagner, M. Gilhaus, D.E. James, CaMKII-mediated phosphorylation of the myosin motor Myo1c is required for insulin-stimulated GLUT4 translocation in adipocytes, Cell Metab. 8 (2008) 384–398.
[137] J. Rieusset, J. Fauconnier, M. Paillard, E. Belaidi, E. Tubbs, M.A. Chauvin, A. Durand, A. Bravard, G. Teixeira, B. Bartosch, M. Michelet, P. Theurey, G. Vial, M. Demion, E. Blond, F. Zoulim, L. Gomez, H. Vidal, A. Lacampagne, M. Ovize, Disruption of cyclophilin D-mediated calcium transfer from the ER to mitochondria contributes to hepatic ER stress and insulin resistance, Hepatology (2012), http://dx.doi.org/10.1002/hep.26189.
[138] N. Joza, J.A. Pospisilik, E. Hangen, T. Hanada, N. Modjtahedi, J.M. Penninger, G. Kroemer, AIF: not just an apoptosis inducing factor, Ann. N. Y. Acad. Sci. 1171 (2009) 2–11.