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Review

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

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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

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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

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