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Insulin resistance and mitochondrial function in skeletal muscle☆

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ABSTRACT

The mechanism(s) behind the decreased ability of insulin to facilitate glucose uptake in insulin sensitive tissues as seen in type 2 diabetes is not resolved. With the rapidly increasing prevalence of this disease world-wide, and the many complications that follow the disease, large resources are used in the attempt to resolve the mechanisms of insulin resistance. In this context, a dysfunction of mitochondria in the skeletal muscle has been suggested to play a pivotal role. It has been postulated that a decrease in the content of mitochondria in the skeletal muscle can explain the insulin resistance. Complementary to this also specific defects of components in the respiratory chain in the mitochondria have been suggested to play a role in insulin resistance. A key element in these mechanistic suggestions is inability to handle substrate fluxes and subsequently an accumulation of ectopic intramyocellular lipids, interfering with insulin signaling.

In this review we will present the prevailing view-points and argue for the unlikelihood of this scenario being instrumental in human insulin resistance.

This article is part of a Directed Issue entitled: Bioenergetic dysfunction.

1. Introduction

In the past decade the idea that mitochondria in skeletal muscle are instrumental in the patophysiology of insulin resistance has been put forward. Since the mitochondria constitute the cell organelles in which the final combustion of nutrients takes place, a dysfunction of the mitochondria (or a lack of sufficient number of functionally intact mitochondria) might be the culprit that causes an accumulation of particularly lipids and carbohydrates both in the intra- and extracellular compartments. This notion may at first glance seem attractive, but it is too simplistic.

Because the terms "mitochondrial function" and "insulin resistance" are central to this discussion, our understanding and definition of these is appropriate to state in the beginning of this review. One fundamental process in the mitochondria is the oxidative phosphorylation (OXPHOS), in which the electrons are removed and transferred from organic molecules to oxygen and the energy released is used in the synthesis of ATP. Measurement and description of this process can be done by measuring the oxygen consumption and/or by measuring the formation of ATP. Often these measurements are referred to as a measurement of mitochondrial function. However, a complete description of the function of mitochondria should cover more than that. The formation of reactive oxygen species (ROS) via incomplete reduction of oxygen, the formation of reactive nitrogen species (RNS) via the reaction of nitric oxide with superoxide, and the activity of the antioxidant system are also important components of mitochondrial function. In the following text, we have therefore written mitochondrial respiratory function when we refer to measurements of oxygen consumption.

Insulin resistance is in the literature defined quite vaguely as a condition that exist whenever normal concentrations of hormone produce a less than the normal biologic response (Kahn, 1978). There is no consensus in the literature on cut-off values, or on the methods for measuring insulin resistance. However, the most accurate method for estimating insulin sensitivity is the hyperinsulinemic glucose-clamp technique (DeFronzo et al., 1979) which is used in the majority of studies on insulin resistance. The technique can be combined with arterio-venous catheterization of the arm or (better) the leg, which is an advantage because insulin resistance predominantly resides in skeletal muscle. Metabolically speaking, the leg consists almost entirely of skeletal muscle. With this technique a precise measure of the insulin mediated glucose uptake can be obtained, dose–response curves can be drawn and the relative level of insulin action between patients and control subjects can be shown. An example of this is shown in Fig. 1.

2. Intramyocellular lipid accumulation

It has been argued that the frequently observed lower mitochondrial content (30–40% lower) in skeletal muscle of patients

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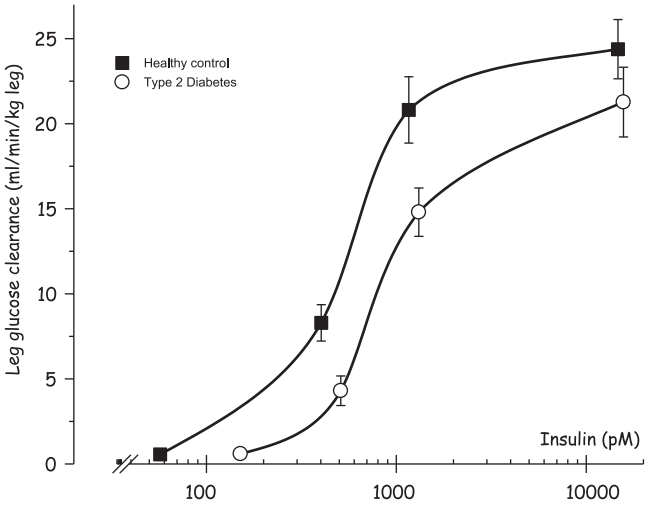

Fig. 1. Insulin mediated glucose clearance rates in leg skeletal muscle. Patients with type 2 diabetes and healthy control subjects had a by a three-step hyperinsulinemic, isoglycemic clamp combined with femoral arterio-venous (a-v) catheterization performed. Glucose clearance rates (glucose a-v concentration difference/arterial glucose concentration × leg blood flow) are shown at basal insulin concentrations and during the following three insulin concentrations. Each clamp step lasted 2 h. The patients with type 2 diabetes display insulin resistance, illustrated as a right- and downward shift of the dose–response curve. Data are taken from a previously published study (Dela et al., 1995) and are shown as mean ± SE.

with insulin resistance constitutes the mechanism by which lipid accumulates in skeletal muscle. The accumulation of lipids in the muscle cell should interfere with insulin signaling, thereby causing insulin resistance (Kelley et al., 2002; Lowell and Shulman, 2005; Morino et al., 2006).

This notion has gained indirect experimental support in studies using magnetic resonance spectroscopy in insulin resistant individuals (Petersen et al., 2004, 2005) showing a decreased ability to generate ATP in the skeletal muscle of these individuals along with increased lipid content of the muscle.

Apart from a methodological concern (Kemp and Brindle, 2012), there are several reasons why this scenario is very doubtful. The first obvious contradiction for likelihood of the idea is the well known fact that athletes accumulate large quantities of intra myocellular triglycerides in their skeletal muscles and yet these individuals are the most insulin sensitive humans (Goodpaster et al., 2001; Dela et al., 1992; Hoppeler et al., 1973). Other lipids than triglyceride (ceramides and diacylglycerol) could potentially also be candidates for interference with insulin signaling. However, studies in humans have revealed that intramyocelullar ceramide content is not associated with insulin resistance (Dube et al., 2011; Helge et al., 2011; Vistisen et al., 2008; Itani et al., 2002; Skovbro et al., 2008) and similar in untrained subjects and athletes (Helge et al., 2004). However, cross-sectional studies in athletes, normal weight and obese sedentary humans (Amati et al., 2011) and in obese humans (Coen et al., 2010; Adams et al., 2004) have linked ceramides with insulin resistance. For diacylglycerol, some studies (Dube et al., 2011; Itani et al., 2002) have found an inverse relationship between changes in the muscle content and insulin sensitivity, but most studies have not been able to demonstrate this (Coen et al., 2010; Vistisen et al., 2008; Amati et al., 2011). Altogether, only a few experimental data exist in favor of the role of lipids in human insulin resistance/sensitivity which is in stark contrast with the many showing the opposite.

3. Skeletal muscle mitochondrial content

The findings of decreased ability to generate ATP in skeletal muscle in insulin resistance is, however, indeed reflected by a roughly similar decrease in maximal respiratory capacity (as per muscle mass) measured in muscle from several different populations of patients with type 2 diabetes (Boushel et al., 2007; Larsen et al., 2009, 2011; Rabol et al., 2010a,b; Hey-Mogensen et al., 2010). In some studies the authors argue in favor of a pivotal role of mitochondrial content (or mass) in skeletal muscle insulin resistance. These studies report a marked decrease in the ability to generate ATP in the skeletal muscle of insulin resistant individuals. Thus, in one study (Petersen et al., 2005) it is shown that insulin resistant humans are almost unable to increase ATP synthesis during insulin stimulation (clamp studies), while the control group increased this synthesis by 90%. Unfortunately, only percent changes in the variables were given with no absolute values which make it difficult to evaluate the findings. However, the reported indirect calorimetric data do support that insulin should almost double ATP synthesis in the control subjects, because energy expenditure was reported to increase by only ~9% (Petersen et al., 2005). In another study (Petersen et al., 2004) mitochondrial rates of ATP production were reduced by ~30% in the muscle of the insulin-resistant subjects ($n = 13$) compared with the control subjects ($n = 10$). However, this difference was apparent because of one single control subject, who displayed an ATP synthesis rate being more than 6 standard deviations above the average values of all other control subjects. At rest, the ATP generation in the skeletal muscle is predominantly used for maintaining the membrane potential and ATP is not accumulated in the muscle. Thus, the production of ATP is accurately adjusted to the need. In this light it is difficult to imagine how the cellular processes overall can be down regulated by ~30% in insulin resistant muscle.

A decreased mitochondrial respiration as per muscle mass (measured by respirometry) or decreased ATP generative capacity (measured by magnetic resonance spectroscopy) seems more likely to be a reflection of the mitochondrial content in the muscle. There is no doubt that the most power full stimulus for mitochondrial biogenesis in skeletal muscle is regularly performed endurance type exercise (Hoppeler et al., 1985). A probable explanation for the decrease in (markers of) mitochondrial content in skeletal muscle of patients with type 2 diabetes may simply be the fact that this disease is to a large extent a lifestyle disease, where imbalance in caloric intake and utilization and in particular lack of exercise in genetically predisposed individuals will facilitate development of insulin resistance, and eventually type 2 diabetes if the pancreatic β-cells are not capable of secreting insulin in the quantity required to maintain euglycemia.

Exercise training studies in patients with type 2 diabetes where mitochondrial content/volume or markers of these have been measured are not plenty. However, there seems to be a consensus that endurance training, also in patients with type 2 diabetes, increase citrate synthase activity (CS) (Hey-Mogensen et al., 2010; Dela et al., 1995) or increase the contents of cardiolipin (Toledo et al., 2007), both of which are valid markers for mitochondrial content in skeletal muscle (Larsen et al., 2012). Moreover, even an increase in protein expression of individual mitochondrial complexes has been shown with endurance training in skeletal muscle (Meex et al., 2010). However, one study did find that patients with type 2 diabetes did not increase the content of several proteins (PDK4, COX1 and COX4) as pronounced as healthy control subjects (Hey-Mogensen et al., 2010). Nevertheless, these studies provide evidence that also patients with type 2 diabetes have the ability to increase their amount of mitochondria in the skeletal muscles. Physical training cannot completely reverse insulin resistance in skeletal muscle (Dela et al., 1995), and after completion of the