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Obesity, Metabolic Syndrome, and Airway Disease: A Bioenergetic Problem?

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SYNOPSIS

Common pathophysiological mechanisms are increasingly being recognized between obesity, metabolic dysfunction, and airway disease. Obesity increases asthma risk or severity, in multiple studies across the globe. Metabolic changes of obesity such as diabetes or insulin resistance are associated with asthma as well as poorer lung function. Insulin resistance has also been found to increase asthma risk independent of body mass. Conversely, asthma has been associated with abnormal glucose and lipid metabolism, insulin resistance, and obesity. These bidirectional and dose-dependent associations suggest common unifying molecular processes that contribute to these seemingly disparate diseases. Reduced mitochondrial mass and/or function is increasingly recognized as one such mechanism that has been causally associated with insulin resistance, obesity and asthma, while conversely, restoration of mitochondrial numbers and function can lead to recovery of normal bioenergetics with reversal of disease features. Here, we review current understanding of how dietary and lifestyle factors lead to changes in mitochondrial metabolism and cellular bioenergetics, inducing various components of the cardiometabolic syndrome as well as airway disease. We provide an overview of and evidence for potentially useful mitochondria-targeted therapies, and discuss the emerging use of mesenchymal stem cells as mitochondrial donors, in the context of asthma.

Keywords

mitochondria; asthma; bioenergetics; reactive oxygen species; metabolic syndrome; arginine; statin; metformin

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INTRODUCTION

Asthma and obesity are twin epidemics in the developed world that are becoming increasingly prevalent globally [1-3]. Not only are obese people at increased risk of asthma, but also asthma in obese individuals does not respond as well to conventional anti-inflammatory therapy, suggesting novel pathogenic mechanisms that contribute to both asthma and obesity: two seemingly disparate diseases [4]. Such mechanisms likely relate to processes that contribute to induction or maintenance of obesity, or to consequences of obesity itself [5,6]. Mitochondrial dysfunction is one such process. Here, we review current understanding of how dietary and lifestyle factors lead to changes in mitochondrial metabolism and cellular bioenergetics, inducing various components of the cardio-metabolic syndrome as well as airway disease. We provide an overview of potential mitochondria-targeted therapies, and discuss the emerging use of mesenchymal stem cells as mitochondrial donors in alleviating disease [7].

BACKGROUND

Optimal cellular bioenergetic function is key to health [8]. It is therefore not surprising that bioenergetic dysfunction is seen in multiple diseases [9-13]. Normally, energy demand of most cells is met through efficient oxidative phosphorylation (OxPhos) reactions that occur in mitochondria [8]. A substantial reserve exists in terms of mitochondrial capacity and optimal concentrations of metabolic substrates such as glucose, permitting a matching of bioenergetic supply to demand. Conversely, inadequate numbers of mitochondria, degradation of mitochondrial function or dysregulated substrate transport are all associated with a bioenergetic “failure” that can occur in disease. What is less clear is whether mitochondrial dysfunction is a trigger for or a consequence of disease. Recently, there has been increasing recognition that bioenergetic failure is not just an outcome of disease, i.e. driven by earlier and/or more upstream mechanisms, but rather a common pathogenesis thread that links together a wide range of co-morbidities that occur in multifactorial diseases such as obesity, metabolic syndrome and asthma [9,14-16]. In this review, we focus on current understanding of bioenergetic changes in obesity, insulin resistance, and asthma; highlighting a functional basis for the intertwined epidemiology. A brief overview of normal mitochondrial metabolism follows in the next section, to provide context for disease-associated changes described subsequently.

PHYSIOLOGY

Cellular bioenergetics takes place largely within the mitochondria, which are semi-autonomous organelles thought to have originated from endosymbiotic relationships between ancient eukaryotic cells and proteobacteria [8,9]. Mitochondria release energy from substrates processed through the tricarboxylic acid (TCA) cycle and electron transport chain (ETC), such that carbon-hydrogen bonds are oxidized to carbon dioxide and water; the liberated energy being captured in the high-energy phosphate bond of adenosinetriphosphate (ATP). The inter-conversion of chemical energy is by nature an inefficient process, and tight coupling between the reactions is necessary to minimize leakage. During the necessary oxygen-dependent ATP production in the ETC, there is some electron leak, leading to the

generation of reactive oxygen species (ROS) as a natural byproduct. ROS, such as superoxide and hydrogen peroxide, are highly reactive molecules that are mutagenic. While low levels of mitochondrial ROS (mtROS) can serve physiologic functions such as signaling, excessive levels from more leaky mitochondria can be detrimental by damaging mitochondrial DNA (mtDNA), critical OxPhos proteins, and oxidizing the lipid membrane. Not only can they cause damage within the mitochondria, thereby setting up a spiraling decline of mitochondrial function, but also can adversely impact other organelles, eventually triggering apoptosis [8,17,18]. Multiple counter-regulatory mechanisms are therefore in place to monitor mitochondrial quality, degrade or disrupt poorly functioning mitochondria, maintain mitochondrial networks, and form new mitochondria as demand increases.

Mitochondrial function is also coupled to bioenergetic demand [19]. ATP, the energy currency, is exported out of mitochondria and circulated within the cell, where energy can be released by controlled hydrolysis of the phosphate bonds, forming di-phosphates (ADP) and mono-phosphates (AMP). Cellular energy reserve and nutrient status is monitored through well-orchestrated machinery, including AMP-sensitive protein kinase (AMPK) and NAD⁺ dependent deacetylase SIRT1, which regulates glucose uptake, autophagy, and mitochondrial biogenesis [19,20]. Further, the mitochondrion is intimately coupled to overall cellular physiology via the mitochondria-associated ER membrane (MAM), which regulates lipid and sterol metabolism and calcium signaling. As a result, mitochondria exhibit “plasticity” i.e. rapid alteration of their numbers and characteristics in response to metabolic fluctuations for meeting cellular needs [19,21,22]. Diet, exercise, insulin, and drugs strongly shape this plastic behavior and consequently mitochondrial health.

Figure 1 illustrates the central role of mitochondria in energy metabolism. High mitochondrial reserve, low baseline ROS production, low burden of mtDNA damage, balanced cellular demand and nutrient supply, and high levels of endogenous ROS scavengers characterize health. It is notable that the inverse occurs seen during natural aging, obesity, and inflammatory disease (Figure 2).

PATHOPHYSIOLOGY

Impact of lifestyle and diet on mitochondrial bioenergetics, insulin resistance, and the metabolic syndrome

Caloric excess and reduced physical activity are increasingly prevalent aspects of the modern lifestyle. Surplus nutrient supply overloads mitochondria [23], leading to overproduction of ROS and accumulation of incompletely oxidized substrates. Damage from these ROS can reduce mitochondrial integrity, triggering their clearance, and can also activate stress pathways that reduce insulin sensitivity and thereby limit nutrient uptake [24,25]. Chronic nutrient oversupply leads to oxidative stress, mitochondrial loss and reduced maximal oxygen consumption. This is exacerbated by physical inactivity, since adaptive mechanisms for increasing mitochondrial activity or mitochondrial biogenesis are strongly related to aerobic exercise [20]. Together, this appears to be the foundation of insulin resistance (IR), and numerous studies in humans and animal models have confirmed that IR is associated with reduced mitochondrial mass or oxidative function in insulin-sensitive tissues. This sets off a vicious feed-forward loop, since insulin action is important

in maintaining mitochondrial metabolism and biogenesis. Since fatty acid oxidation for energy can only happen in mitochondria, fats are not adequately metabolized, leading to intracellular accumulation as well as increased circulating lipids. Hyperinsulinemia is the primary compensatory response to insulin-resistance in the principal glucose utilizing organs such as liver and skeletal muscle, creating beta cell stress and eventually secretory deficiency. Together this forms the basis for the triad of obesity, dyslipidemia and hyperglycemia, namely the metabolic syndrome (MetS).

MetS, especially obesity, represents a strong risk factor for asthma [3,26]. Hyperinsulinemia seems to be an independent risk factor in some studies and we have previously reviewed how hyperinsulinemia may lead to changes in the lung characteristic of asthma via growth factor-like effects and increased PI3/Akt signaling [27]. Recently, a vagally-mediated bronchoconstrictor effect of hyperinsulinemia has also been described [28]. These associations form the basis of exploring whether and how mitochondrial mechanisms important in MetS can also contribute to asthma.

In the cascade of events described above, the key initiator is mitochondrial dysfunction due to caloric excesses and physical inactivity. So far there is no clear evidence that this is related to mitochondrial genome variations although some mtDNA polymorphisms are associated with metabolic syndrome components [29]. While the ratio of mitochondrial DNA to nuclear DNA is markedly reduced in metabolic syndrome, it is not associated with any major genomic deletions and most likely simply represents increased damage, accelerated clearance and, importantly reduced mitochondrial biogenesis [30,31]. The resultant mitochondrial dysfunction, especially in key insulin-sensitive tissues like liver and muscle, potentiates hyperinsulinemia and obesity, which increase asthma risk through a number of pathways as discussed in this special issue and also elsewhere [3,5,6]. Restricting calories and maintaining physically active lifestyles protect against such mitochondrial dysfunction, lead to weight loss, and have been shown to improve asthma [4]. However, beyond this indirect link between MetS, mitochondrial dysfunction and asthma that is mediated by obesity and insulin resistance, there is also a much more direct link within the lung.

Mitochondrial Dysfunction and Asthma

As far back as 1985, it had been described that human bronchial epithelial cells of asthmatics showed swollen mitochondria [32]. Mabalirajan and colleagues dissected this further in experimental mouse models of allergic airway inflammation and found this to be an integral part of the asthma phenotype [33] [34]. Key inflammatory cytokines associated with asthma such as interleukin-4 (IL-4) and IL-13 have been found to induce mitochondrial dysfunction via upregulation of the oxidized linoleic acid metabolite, 13-S-HODE [34-36]. Also, allergic airway inflammation has been associated with increase in asymmetric dimethyl arginine (ADMA), an endogenous methyl-arginine that uncouples nitric oxide synthase, leading to ROS formation and mitochondrial dysfunction [37,38]. Interestingly, ADMA is also increased in obesity due to increased protein turnover [6]. A causal role for mitochondrial dysfunction was further suggested by studies in mice with a genetic deficiency of mitochondrial ubiquinolcytochrome C-reductase-core-II protein in the airway

epithelium [39]. These mice, which have airway mitochondrial dysfunction, exhibited much greater inflammation and airway remodeling than normal mice upon allergen sensitization and challenge [39]. In other work, treatment of mice with low dose inhaled rotenone, an ETC blocker, led to features of airway remodeling and hyperresponsiveness [7]. Importantly, both mice treated with rotenone and those with allergic airway inflammation, show marked attenuation of asthmatic features if mitochondrial function is restored. This will be discussed further in the section on mitochondria-targeted therapeutics.

Currently there is limited human evidence for a causal role of mitochondrial dysfunction in asthma. However, human genetic studies of asthma are suggestive of a mitochondrial component [40]. While there are no consistent reports of mitochondrial mutations in asthma, vertical transmission from mothers has been reported along with some genetic associations [41-43]. Mutations in genes encoding mitochondrial tRNAs and the ATP synthase mitochondrial F1 complex assembly factor 1 gene have been associated with childhood asthma. This evidence, together with experimental observations, suggest a direct role of mitochondrial dysfunction in asthma pathogenesis. What is less clear is which aspects of mitochondrial function or dysfunction contribute to human asthma phenotype, particularly along the spectrum of mild through severe asthma. It also remains unclear whether mitochondria contribute to the sensitivity or resistance of asthmatic airways to existing therapies such as corticosteroids. It is well known that mitochondria have a complex morphology due to highly regulated fission and fusion and normally form an intricate tubulo-reticular branched network [14,44]. It is now also apparent that this structure has multiple and far-reaching implications, including protecting mitochondrial stability, respiratory functions, cell fate determination, and adaptation to cellular stress. We have seen that mitochondrial fragmentation and other morphological changes occur during allergic asthma or cigarette smoke exposure or diet- induced obesity [14,45]. These are not fully reversed by anti-inflammatory therapy and may contribute to progressive disease.

Mitochondrial dysfunction and Chronic Obstructive Pulmonary Disease (COPD)

Cigarette smoking as well as second-hand exposure increases the risk or severity of asthma as well as COPD. Short term as well as longer exposure to cigarette smoke (CS) has been shown to induce mitochondrial dysfunction [46,47]. This is accompanied by increased mitochondrial network fragmentation and ROS generation, which can be perpetuated by cell signaling pathways such as ERK, PI3/Akt, PKC and transcriptional regulation by NF κ B and Nrf2 [14]. This represents an important intersection between asthma and COPD since airway smooth muscle (ASM) cells from asthmatics show such fragmentation and ROS generation at baseline, which is further enhanced by CS [14]. Oxidative stress is well known as an important part of asthma and COPD pathogenesis and there is well-known mitochondrial pathology in skeletal muscle of COPD patients [9,48]. It seems likely, therefore, that cigarette smoke-induced mitochondrial dysfunction potentiates oxidative stress in lung, contributing to cell senescence and apoptosis. These represent a form of accelerated aging of the lung, which has been recently implicated in the genesis of COPD [49-51]

TREATMENT

At this time, there is no specific approved therapy for mitochondrial dysfunction or separate treatment guidelines for obese patients with asthma. There is, however, increasing recognition that such obese-asthma is clinically different and may not respond fully to convention anti-inflammatory therapy (see review by Sherry Farzan in this issue). The accompanying review by Nijra Lugogo describes the role of weight loss in the management of asthma and evaluates the evidence for bariatric surgery in obese-asthma. Here we briefly focus on therapies that are associated with improvement in mitochondrial function and have been shown to have potential benefit in metabolic syndrome and asthma (Figure 3).

Lifestyle modification and weight loss should be first-line recommendations in obese-asthma since these have general health benefits. Exercise and caloric restriction (CR) have been shown to enhance natural antioxidant scavengers, reduce mtROS, promote mitochondrial biogenesis, and slow aging [20,52,53]. However, it is also possible that CR may not be acceptable to the patient and exercise capacity may be impaired by the combination of asthma and obesity. Accordingly, while diet and lifestyle changes can have substantial beneficial effects in the context of asthma, more directed therapies are needed.

One approach towards chemically mimicking CR is to administer metformin, which via its actions on AMPK, restores insulin sensitivity and promotes mitochondrial metabolism [54]. Metformin is already the treatment of choice for diabetes and is being considered for use in obese non-diabetics [55]. In mice with high-fat diet induced obesity, metformin attenuates allergen-induced eosinophilic inflammation [56]. Metformin-treated animals behaved similarly to lean controls, hastening the resolution of inflammation. Anti-asthma effects of metformin were also previously noted in other allergen models of asthma [57], but not in genetically obese mice with intrinsic airway hyperresponsiveness or ozone-induced inflammation [58]. This suggests that the beneficial effects of metformin are through common metabolic processes between allergic asthma and dietary obesity although these remain to be fully characterized.

Nitric oxide metabolism is impaired in obesity and metabolic syndrome due to increased methyl-arginines such as ADMA and reduced L-arginine bioavailability. These have also been strongly implicated in mitochondrial dysfunction and asthma. We have previously shown that supplementation of L-arginine not only benefits cardiovascular aspects of the metabolic syndrome, but also attenuates mitochondrial dysfunction and asthma features in experimental models [37,59]. Similar effects on nitric oxide metabolism and asthma were obtained by inhibition of L-arginine degradation by arginase [60] or by statin mediated restoration of eNOS levels and degrading of ADMA [61]. Even metformin has important effects of nitric oxide metabolism, suggesting that this may be a critical common interface between obesity and asthma. These drugs are now in clinical trial for asthma and the accompanying review by Nicholas Kenyon, on novel therapeutic strategies for obese-asthma, provides more detail.

Exogenous antioxidants to scavenge ROS, inhibitors of 12/15 lipoxygenase (baicalein and esculetin) to reduce mitotoxicity, and sirtuin activators such as resveratrol to stimulate

mitochondrial biogenesis have all been found to attenuate experimental asthma [44,62-65]. While these pathways are also implicated in obesity and metabolic syndrome, any benefits of these strategies in obese-asthma remain to be ascertained.

Mitochondria targeted antioxidants are also of potential benefit. Coenzyme Q10 (CoQ10), also known as ubiquinone, is a component of the ETC and can therefore exist in both fully oxidized and reduced states, making it a powerful mitochondria-targeted antioxidant [66]. In a small study of fifty-six asthmatics, Gazdik and colleagues reported reduction of CoQ10 in plasma and whole blood [67]. In a subsequent open-label crossover study of forty-one steroid-dependent asthma patients, they found that supplementation with a daily antioxidant cocktail, consisting of CoQ(10) (120 mg) + 400 mg alpha-tocopherol + 250 mg vitamin C, was associated with a reduction in steroid usage [68]. Since glucocorticoids can induce mitochondrial dysfunction and are relatively ineffective in obese-asthma, this is potentially important. CoQ supplementation has also been variably found to be beneficial in cardiac components of the metabolic syndrome [69]. However, supplementation with other exogenous antioxidants like alpha-tocopherol and vitamin C have not been successful and there are conflicting reports including interference with mitochondrial signaling and biogenesis [70]. Thus mitochondria targeted antioxidants such as CoQ10 and its modified forms (MitoQ) merit further investigation in the treatment of obese asthma [71]

One limitation of any mitochondrial-targeted therapy in asthma is that mitochondrial numbers and dysfunction in different cell types may have different implications and may even be a double-edged sword [9,14,72]. For example, ROS produced during fatty acid oxidation in mitochondria suppress the inflammatory Th17 lymphocyte polarization and dominant fatty acid metabolism promotes formation of regulatory T cells (Treg) that have important anti-inflammatory function [72]. Thus normal mitochondrial ROS generation can be beneficial and antioxidant therapy may not always be helpful. However, airway epithelial cells from allergically inflamed lungs show increased ROS, mitochondrial dysfunction and a reduction in mitochondrial biogenesis [7]. The ASM shows increased mitochondrial fission, dysfunctional mitochondrial network formation and increased ROS, although the biogenesis may be increased [7,14]. Together these promote the aberrant fibrotic and hypercontractile pathology of asthma that is characterized by epithelial injury, but ASM and fibroblast proliferation. An additional layer of cell-type specific targeting, either through delivery routes and carriers, or through novel biologicals, may be required to specifically target mitochondrial function.

SUMMARY AND FUTURE DIRECTIONS

Both obesity and asthma share common metabolic derangements that intersect at the level of mitochondrial function. It is likely that the mitochondrial dysfunction of insulin resistance or obesity increases asthma incidence or severity. Conversely, asthma associated mitochondrial dysfunction may lead to systemic metabolic changes that promote insulin resistance and obesity [73]. A number of clinical trials are now in progress for evaluation of metabolic drugs like metformin, statins, and l-arginine in asthma and the results are awaited. Mitochondrial targeted antioxidants like coenzyme Q10 and MitoQ also show promise. Until recently there were no strategies for replenishing healthy mitochondria and restoring

normal bioenergetics by exogenous donation. However, recent work from Jahar Bhattacharya's lab [74] and the Agrawal lab [7] shows that exogenous mesenchymal stem cells can donate mitochondria to lung epithelium, restoring bioenergetic function and attenuating inflammation and injury. This transfer appears to be regulated by Miro1 and MSC overexpressing Miro1 are effective in reversing asthmatic airway remodeling and hyperresponsiveness [7]. This is being explored further in models of diet induced obesity, metabolic syndrome, and asthma and represents an entirely new direction for the future (Figure 4).

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Key Points

1. Mitochondrial dysfunction increases severity or risk of asthma.
2. Caloric excesses and reduced physical activity lead to insulin resistance, obesity, and the metabolic syndrome through abnormal mitochondrial bioenergetics.
3. Caloric restriction and aerobic exercise promote mitochondrial biogenesis and improve bioenergetics. Metformin treatment recapitulates some of the effects of caloric restriction.
4. Mitochondrial targeted antioxidants like coenzyme Q10 and MitoQ may be beneficial in severe asthma.

Figure 1. Mitochondrial function in health

Mitochondria are the powerhouses of cells. The tricarboxylic/citric acid cycle (TCA) and electron transport chain (ETC) work in conjunction with glycolysis and fatty acid oxidation to extract the energy stored in carbon-hydrogen bonds and store it in ATP, which is the energy currency of the cell. Reactive oxygen species (ROS) are generated during flow of electrons across ETC, which are scavenged by local antioxidants. A low level of ROS is important in cell signaling and other than ATP production, mitochondria also participate in calcium regulation and steroid synthesis.

Figure 2.

Mitochondrial dysfunction is a common point of convergence during normal aging or pathological stress. Activation of NADPH oxidase (NOX) or 12/15 Lipoxygenase (LOX) is an important trigger for lipid peroxidation during inflammatory states. Increased ROS generation due to nutrient excess or accumulation of damage with age can lead to similar endpoints.

Therapies associated with improvement in mitochondrial function

Figure 3.
Reversing bioenergetic failure in obesity and asthma.

Figure 4.

Mesenchymal stem cells are potential mitochondrial donors that transfer healthy mitochondria via intercellular nanotubes to stressed epithelial cells. In experimental models, this has been associated with anti-asthma effects.