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REVIEW ARTICLE

MITOCHONDRIA AS THERAPEUTIC TARGETS

Mitochondria As Therapeutic Targets for Insulin Resistance and Type 2 Diabetes

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Abstract

Insulin resistance is a hallmark of type 2 diabetes mellitus (T2DM), characterized by impaired insulin action in target tissues, leading to dysregulated glucose metabolism and metabolic dysfunction. Mitochondrial dysfunction has emerged as a central player in the pathogenesis of insulin resistance, influencing cellular bioenergetics, oxidative stress, and inflammatory responses. This review provides an overview of the intricate interplay between mitochondria and insulin resistance in T2DM, highlighting the molecular mechanisms involved and exploring the therapeutic potential of targeting mitochondria to improve insulin sensitivity and glycemic control. We discuss recent advances in our understanding of mitochondrial dysfunction in insulin resistance, including alterations in mitochondrial structure, function, and dynamics, as well as the signaling pathways linking mitochondrial dysfunction to impaired insulin action. Furthermore, we examine various mitochondria-targeted interventions, such as mitochondrial antioxidants, modulators of mitochondrial biogenesis, mitophagy enhancers, and agents targeting mitochondrial dynamics, and their efficacy in preclinical insulin resistance and T2DM models.

Keywords: *Mitochondria, Insulin resistance, Oxidative stress, Mitochondrial biogenesis*

1 Introduction

Insulin resistance refers to a condition wherein peripheral tissues exhibit a diminished response to insulin(1), resulting in impaired regulation of glucose uptake and metabolism, consequently leading to elevated blood glucose levels. This condition leads to a pivotal factor in the pathogenesis of type 2 diabetes mellitus (T2DM)(2). Numerous studies have underscored a robust association between insulin resistance and the risk of developing T2DM(3). It is widely believed that insulin resistance comes from a combination of genetic and lifestyle factors such as obesity and physical inactivity, and certain medical conditions like polycystic ovary syndrome, as well as the use of specific medications(4). Insulin resistance is a crucial component of various metabolic disorders, such as obesity and type 2 diabetes(5). It is characterized by a decreased response to insulin, leading to impaired glucose uptake and metabolism in target tissues such as skeletal muscle and adipocytes(4). Importantly, insulin resistance may cause insufficient insulin production by the pancreatic β-cells, thereby progressing to T2DM. Often, insulin resistance coexists with other metabolic abnormalities, including dyslipidemia and hypertension, further increasing the risk of cardiovascular disease, a major complication of T2DM(6). Recent studies have shed light on the potential link between mitochondrial dysfunction and insulin resistance(5; 7). These studies have shown that compromised mitochondrial oxidative function in skeletal muscle may contribute to excess lipid accumulation and the development of insulin resistance(7). This link between mitochondrial dysfunction and insulin resistance is supported by evidence of impaired fatty acid oxidation, which leads to the buildup of lipid metabolites such as ceramide and diacylglycerol. These lipid metabolites have been shown to interfere with insulin signal transduction, further exacerbating insulin resistance(5; 8). Furthermore, research has indicated that mitochondrial health and function play a crucial role in regulating insulin sensitivity. Specifically, the ability of mitochondria to adapt to available metabolic fuels, regulate mitochondrial biogenesis, and undergo post-translational modifications of proteins involved in mitochondrial bioenergetics all contribute to insulin sensitivity(7). Mitochondria,

known as the powerhouses of cells, play a critical role in cellular energy production and metabolism(9). These organelles are responsible for oxidizing substrates and generating ATP through oxidative phosphorylation. However, when structural and functional alterations occur in mitochondria, they can have profound effects on cellular homeostasis and contribute to the development of various clinical disorders and neuropsychiatric abnormalities including type 2 diabetes(9; 10). Mitochondria are essential organelles involved in various cellular processes, including energy production, metabolism, and cell signaling(11). They play a crucial role in maintaining cellular homeostasis and promoting cell survival(12). Targeting mitochondria for therapeutic intervention offers a novel and potentially transformative approach to managing chronic diseases(9). By improving mitochondrial function or preventing mitochondrial energy failure, it may be possible to address the underlying abnormalities that contribute to a broad range of clinical disorders(13).

2 Mitochondrial Dysfunction

Mitochondrial dysfunction refers to the impaired or disrupted functioning of mitochondria, which are small organelles found within cells that are responsible for producing energy in the form of ATP(14). This dysfunction can occur due to various factors, such as genetic mutations, environmental toxins, or oxidative stress. Furthermore, this dysfunction can lead to a decrease in ATP production, an increase in reactive oxygen species generation, and disruptions in calcium buffering and other cellular processes(15). As a result, mitochondrial dysfunction has been implicated in the pathogenesis of numerous diseases, including diabetes(9; 14). Extensive research has been conducted to understand the precise mechanisms underlying mitochondrial dysfunction in these diseases, but a definitive explanation has not yet been established(16). However, it is clear that mitochondrial dysfunction plays a significant role in the development and progression of these conditions(17). In recent years, there has been growing interest in targeting mitochondrial processes, pathways, and proteins for drug discovery efforts in various diseases, including cancer, cardiovascular diseases, metabolic disorders, and central nervous system diseases(16). Mitochondrial dysfunction is a common feature in many diseases, including diabetes and neurodegenerative disorders like Alzheimer's and Parkinson's(17). Furthermore, research has shown that mitochondrial dysfunction leads to an increase in oxidative damage, causing harm to DNA, RNA, proteins, and lipids. The importance of understanding and targeting mitochondrial dysfunction as a therapeutic strategy has been recognized in the field of research and drug discovery.

3 Molecular Mechanisms Linking Mitochondrial Dysfunction to Insulin Resistance

Molecular mechanisms linking mitochondrial dysfunction to insulin resistance have been the subject of extensive research in recent years(17). During the past two decades, lines of evidence suggest that mitochondrial dysfunction plays a key role in the pathophysiology of diabetes. Mitochondrial dysfunction in diabetes is associated with insulin resistance, where defects in mitochondrial function contribute to impaired glucose metabolism and decreased insulin sensitivity. These defects at the mitochondrial level can be caused by various genetic and environmental factors, leading to disruptions in energy metabolism and glucose-stimulated insulin secretion. As a consequence of mitochondrial dysfunction, there is an increase in the production of reactive oxygen species which can lead to oxidative damage to cellular components(14).

4 Role of Oxidative Stress in Impairing Mitochondrial Function in Diabetes

Oxidative stress, which is a major trigger for the development of diabetes and its consequences, is defined by excessive ROS generation and intracellular oxidative damage. Oxidative stress is defined as an imbalance of two opposing and antagonistic forces: the generation of ROS and antioxidants, in which the harmful effects of ROS outweigh the compensating impact of antioxidants in cells(18) This imbalance can be triggered by high blood sugar levels, as glucose metabolism generates reactive oxygen species. These reactive oxygen species can damage cellular structures, including mitochondria, which are responsible for producing energy in the cell. Mitochondrial dysfunction in diabetes is characterized by impaired ATP production, increased reactive oxygen species production, and altered mitochondrial morphology and dynamics. This disruption in mitochondrial function and oxidative stress can further exacerbate the development and progression of diabetes. Due to their inadequately linked electron transport, mitochondria are the main generator of reactive oxygen species (ROS) in cells. Because of the elevated generation of free radicals and weakened antioxidant defenses, oxidative stress is well acknowledged as a major mediatory factor in the onset, course, and consequences of diabetes(19; 20). Increased glucose levels promote the overproduction of ROS, which causes morphological abnormalities in mitochondria(21). The respiratory chain's redox status is the fundamental determinant of mitochondrial ROS production(22). The dominant view is that hyperglycemia causes an increase in electron transfer donors (NADH and FADH2), which increases electron flow across the mitochondrial electron transport chain. As a result, the ATP/ADP ratio increases, and the mitochondrial membrane potential becomes hyperpolarized. The significant electrochemical potential difference caused by the proton gradient partially inhibits electron transit in complex III, resulting in electron buildup at coenzyme Q. As a result, O2 undergoes partial reduction, producing the free radical anion superoxide(23). This rapid loss of coenzyme Q and formation of ROS is thought to be the primary cause of mitochondrial malfunction, which plays a significant role in diabetes-related metabolic diseases(24).

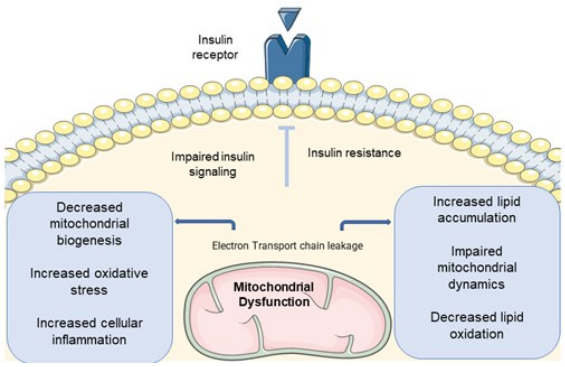

Figure 1: Representation of Mechanism of Mitochondrial Dysfunction Leading to Insulin Resistance

5 Mitochondrial-Derived Metabolites on Cellular Inflammation and Insulin Sensitivity

Current research has discovered that open reading frame locations in human mitochondrial rRNA may encode and produce polypeptides known as mitochondrial-derived peptides (MDPs). MDPs can be used as a new type of reverse signal molecule, allowing the cell to retrogradely pass signals to the nucleus during stress, regulating gene transcription synthesis, exerting anti-inflammatory and antiapoptotic effects, and promoting the synthesis of mitochondrial biological effects, all of which influence the development of diabetes and its complications(25). Current studies have showed that, by targeting skeletal muscle, MDPs have a moderating impact on insulin resistance and promote glucose absorption into the pentose phosphate route, avoiding hepatotoxicity caused by medications such as metformin(26). Humanin can bind insulin-like growth factor binding protein 3 Humanin's entrance into the ventricle increases insulin sensitivity in the liver and muscle, resulting in less glucose synthesis in the liver and more insulin-mediated Akt and fatty acid metabolism signaling(27). Humanin also enhances peripheral glucose uptake and inhibits liver glucose production(28). MOTS-c targets skeletal muscle, which can increase systemic insulin sensitivity, glucose processing rate, and muscle-mediated AMPK activation and GLUT4 expression. In 2015, (25) discovered that MOTS-c may improve AMPK activation and GLUT4 expression under the high-fat diet (HFD), enhance systemic insulin sensitivity through muscle, and raise the glucose processing rate of insulin stimulation(25). In addition, (29) discovered that in mice infected with methicillin-resistant Staphylococcus aureus (MRSA), MOTS-c increased macrophage phagocytosis and bactericidal ability by suppressing MAPK, increasing expression of the negative regulator of inflammation AHR, and phosphorylating STAT3. Pro-inflammatory cytokines TNF-α, IL-6, and IL-1β decreased, whereas anti-inflammatory cytokine IL-10 increased(29).

6 Mitochondrial Dynamics in Modulating Insulin Action and Glucose Homeostasis

Mitochondrial dynamics, the fusion and fission events that occur within mitochondria, play a crucial role in modulating insulin action and glucose homeostasis(9). These events are essential for maintaining the mitochondrial population and ensuring the stability of mitochondrial DNA, as well as the respiratory capacity of the cell. Abnormalities in mitochondrial dynamics have been linked to insulin resistance and type 2 diabetes in both humans and animal models. Furthermore, mitochondrial dynamics are involved in the balance between energy demand and nutrient supply, making them crucial for overall metabolic function(30). Additionally, mitochondria generate reactive oxygen species as a byproduct of fuel oxidation, which have been implicated in the pathophysiology of diabetes and its complications. Therefore, understanding the role of mitochondrial dynamics in insulin action and glucose homeostasis may provide valuable insights into the development of new treatment and prevention strategies for diabetes and metabolic diseases(30). Mitochondria constitute a complex dynamic network that is constantly undergoing fusion and fission events, referred to as mitochondrial dynamics (mtDYN). Mitochondrial dynamics is a quality control mechanism necessary for sustaining the mitochondrial population, relevant to the integrity of mitochondrial DNA (mtDNA), respiratory capacity, and cell response to stress(31). During physiological settings, mitochondria undergo morphological modifications in order to meet cellular energy demands. These alterations can occur as a result of ongoing cycles of mitochondrial fusion and fission, allowing for proper mitochondria distribution inside cells. Thus, mitochondria are not static organelles; they alter form and position in response to physiological stimuli. Mitochondrial fission produces small individual mitochondria, whereas fusion generates huge linked mitochondrial networks(32). Mitochondrial dynamics is critical for type 2 diabetes and associated vascular consequences. In reality, mitochondria are master controllers of insulin production, and mtDNA alterations have been linked to the development of type II diabetes. In fact, a new mutation m.8561 C>G in MT-ATP6/8 (subunits of mitochondrial ATP synthase) was recently identified to induce diabetes mellitus and hypergonadotropic hypogonadism(33).

7 Mitochondria-Targeted Interventions for Improving Insulin Sensitivity

Potential approach to improve insulin sensitivity is through mitochondria-targeted interventions(34). These interventions aim to specifically target and optimize the function of mitochondria, the "powerhouses" of our cells, in order to enhance insulin signaling and promote better glucose metabolism. Some potential mitochondria-targeted interventions include the use of small molecules that can enhance mitochondrial function, improve oxidative phosphorylation, and regulate lipid homeostasis(35). Additionally, certain drugs and hormone therapies have been shown to affect mitochondrial function and may be considered as potential

interventions for improving insulin sensitivity. These interventions hold promise for the development of novel agents for diabetes therapy and may provide new avenues for research and treatment in the field of metabolic disorders.

8 Targeting Mitochondrial Biogenesis

Mitochondrial biogenesis is the process by which mitochondria regenerate, which is necessary for preserving their integrity. New mitochondria are formed from existing mitochondria through two highly controlled processes: fusion and fission(36). Under normal physiological conditions, mammalian cells maintain a dynamic equilibrium of fission and fusion. Disruption of this fission-fusion equilibrium affects mitochondrial shape; excessive fission leads in fragmented mitochondria, whereas excessive fusion results in elongated mitochondrial tubules(37). Peroxisome proliferator-activated receptor gamma coactivator-1a (PGC-1α) is a key regulator of mitochondrial biogenesis, according to many lines of evidence. PGC-1α is deacetylated and activated by Sirtuin 1 (SIRT1), a nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylase. PGC-1α assists in coordinating the expression of genes involved in aerobic metabolism with a network of transcription factors. A number of nuclear genes that code for mitochondrial enzymes are regulated by PGC-1α. These in turn promote the production of other transcription factors, such as nuclear respiratory factor-1 (NRF1) and NRF2, that are involved in the coordinated regulation of mitochondrial genes. Nuclear genes encoding proteins involved in transcription and mtDNA replication as well as polypeptides of the respiratory chain are expressed in response to NRF1 and NRF2(38; 39). Insulin sensitization is caused by thiazolidenediones like pioglitazone, which also raise the amount of mitochondrial DNA copies and PGC-1α expression in white adipose tissue(40). Overall increase in the mitochondrial biogenesis can and improving mitochondrial content can reverse the insulin resistance and improves mitochondrial dysfunction associated insulin resistance.

9 Mitochondrial Antioxidants: Role in Reducing Oxidative Stress and Improving Insulin Sensitivity

Mitochondrial antioxidants play a crucial role in reducing oxidative stress and improving insulin sensitivity, making them potential therapeutic targets for managing diabetes and metabolic disorders. These antioxidants help combat the excessive production of reactive oxygen species in mitochondria, which is often elevated in conditions like insulin resistance and diabetes(41). They do this by neutralizing harmful free radicals and preventing oxidative damage to mitochondrial proteins and DNA. Abundant evidence has been accumulated to show the importance of reversible acetylation/deacetylation of mitochondrial proteins through the action of SIRT3 and its potential role in the development of insulin resistance and metabolic disorders. Thus, targeting the acetylation status of mitochondrial proteins and enhancing the activity of SIRT3 may be a promising strategy for restoring normal cellular redox status and improving insulin sensitivity in individuals with diabetes and insulin resistance(42). In addition, researchers have found that mitochondrial antioxidants have the ability to improve insulin sensitivity by regulating mitochondrial function and redox status. They do this by enhancing the efficiency of ATP production, reducing oxidative damage, and improving insulin signaling pathways(43). Moreover, recent studies have shown that impaired mitochondrial function and increased reactive oxygen species production contribute to the pathogenesis of insulin resistance and metabolic disorders. Therefore, targeting mitochondrial antioxidants may be a potential therapeutic approach to reduce oxidative stress and improve insulin sensitivity in these conditions.

10 Conclusion

Insulin resistance, a hallmark of type 2 diabetes mellitus (T2DM), is characterized by the impaired response of target tissues to insulin, leading to disrupted glucose metabolism and overall metabolic dysfunction. Mitochondrial dysfunction has emerged as a crucial factor in the development of insulin resistance, influencing cellular bioenergetics, oxidative stress, and inflammation. This review has highlighted the complex interplay between mitochondrial dysfunction and insulin resistance, detailing the molecular mechanisms involved and exploring potential therapeutic strategies targeting mitochondria to improve insulin sensitivity and glycemic control. Recent research has deepened our understanding of how alterations in mitochondrial structure, function, and dynamics contribute to insulin resistance. Mitochondrial dysfunction, characterized by impaired oxidative phosphorylation, increased production of reactive oxygen species, and disrupted mitochondrial dynamics, interferes with insulin signaling and glucose homeostasis. This review also examined various mitochondria-targeted interventions, such as mitochondrial antioxidants, modulators of mitochondrial biogenesis, mitophagy enhancers, and agents targeting mitochondrial dynamics. These interventions have shown promise in preclinical models for enhancing insulin sensitivity and managing T2DM. The exploration of mitochondria as therapeutic targets offers a novel and potentially transformative approach to managing insulin resistance and T2DM. By improving mitochondrial function or preventing mitochondrial dysfunction, it may be possible to address the underlying abnormalities that contribute to these metabolic disorders. Future research should focus on translating these findings into clinical practice, developing effective mitochondria-targeted therapies, and evaluating their long-term benefits and safety in patients with T2DM.

Conflict of Interest

The authors declare no conflict of interest in this reported communication.

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