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Literature Reviews

Mitochondrial Dysfunction Model in the Pathogenesis of Inflammatory Response Development in Obesity

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Abstract: Obesity is one of the growing problems of modern society. Although currently used methods of treating obesity, including diet, exercise, and drug therapy, have shown their applicability to more effectively combat obesity, an understanding of the pathogenesis of this disease is required. One of the insufficiently studied factors in the pathogenesis of obesity is the development of mitochondrial dysfunction understanding the role of which in the development of obesity will make it possible to find new ways to combat this disease. The review was created by analyzing evidence from the most promising studies on the pathogenesis of obesity. The main aim of this review was to develop a model of the pathogenesis of obesity, the central link in which is the development of mitochondrial dysfunction. An additional aim was to propose, based on the developed model, a number of potential therapeutic strategies for the treatment of obesity. Increased nutrient intake leads to the disruption of the electron transport chain work, which causes an increase in the production of reactive oxygen species, which causes: (1) Damage to mitochondria and as a result, mitochondrial dysfunction, impaired energy metabolism, and increasing oxidative stress, (2) As well as damage to other cellular structures and as a result, the accumulation of toxic oxidation products and immunogenic molecules. Together, this leads to chronic inflammation and the development of insulin resistance, which is the high-risk factor for diabetes. Compounds aimed at normalizing the function of mitochondria, such as L-carnitine and ubiquinone, can be proposed as additional therapies. Aerobic exercise also contributes to the normalization of mitochondrial function.

Keywords: Mitochondrial Dysfunction, Mitochondria, Pathogenesis, Obesity, Reactive Oxygen Species

Introduction

Obesity is the excessive accumulation of fat in the body, which can lead to serious deterioration in health. The simplest, but not sufficiently accurate indicator of the diagnosis of obesity is the body mass index which is the index of the ratio of body weight to height. It is defined as a person's weight in kilograms divided by their height squared. A person is considered obese with a body mass index greater than or equal to 30 (WHO, 2021). The number of people with obesity is increasing every year: Between 1975 and 2016, the prevalence of obesity worldwide almost tripled and exceeded one billion cases, of which more than 300 million cases of obesity occurred in children (WHO, 2021). Obesity is dangerous because it has been proven to increase the risk of developing various serious diseases, such as hypertension, type 2 diabetes, cardiovascular disease, osteoarthritis, liver disease, kidney failure, and several forms of cancer (Martin-Rodriguez *et al*., 2015). Obesity begins to manifest itself with a long-term strong surplus of calories consumed, so the main reasons for its development are excessive consumption of high-calorie foods in fat and fast carbohydrates, as well as the consumption of sugary drinks, which are often overlooked as a source of calories and a sedentary lifestyle, which does not allow the excess of consumed energy to be spent (WHO, 2021). Other factors in the development of obesity include hormonal disorders, disruption of the gut microbiome, and neuroendocrine

diseases, as well as genetic factors, but it should be understood that most often the development of obesity is associated with the interaction of several factors (Kaila and Raman, 2008; Mayo, 2023).

While natural means to create a long-term calorie deficit such as increased physical activity and dietary changes are logical measures to combat obesity, they are often not effective enough. The reason for this is the established sedentary lifestyle with the consumption of large amounts of high-fat foods, so it can be difficult for the patient to diet and exercise if they have not done so before and the patient himself is often the sole controller of treatment in this case. It is also worth noting that in patients with a 3rd degree of obesity (with a body mass index of more than 40), it is often difficult to perform even simple physical exercises. From this, it follows that medical care is an additional auxiliary means of therapy. To date, several drugs have been developed that have shown effectiveness in the treatment of obesity. So, Sibutramine inhibits the reuptake of norepinephrine and serotonin, which leads to a decrease in appetite (Kaila and Raman, 2008). Orlistat is a strong inhibitor of gastric and pancreatic lipases; it can reduce the absorption of dietary fats by up to 30% (Kaila and Raman, 2008). Lorcaserin acts on the feeling of satiety through the brain: This drug activates the serotonin 5-HT2C receptor located in the hypothalamus (Youdim, 2021).

Understanding the processes at the cellular and molecular level that are associated with the pathogenesis of obesity can help create new types of drugs that can achieve better results in combination with existing therapies. As will be described below, the pathogenesis of obesity is associated, among other things, with the development of an inflammatory response. Inflammation plays a significant role in the pathogenesis of many types of diseases and one of the links in the development of inflammation may be a disruption in the functioning of mitochondria (Van Horssen *et al*., 2019).

It is considered that the development of chronic inflammation in obesity is a risk factor leading to the development of diabetes mellitus, atherosclerosis, and a number of other chronic diseases (Ellulu *et al*., 2017). One of the properties of the pathogenesis of obesity is the combination of impaired metabolism with the development of a weak inflammatory response. Since mitochondrial dysfunction is the cause of energy metabolism disorders and also leads to the development of an inflammatory response, in this review a model has been compiled that combines metabolic and inflammatory processes into a common pathological scheme of obesity based on mitochondrial dysfunction. The development of such a pathological model is the uniqueness of this review, which distinguishes this study from similar reviews in which mitochondrial dysfunction in obesity has been investigated by providing useful but separate facts (Bournat and Brown, 2010; Lefranc *et al*., 2018). The described pathological model will make it possible to identify key trigger points in the pathogenesis of obesity, which will contribute to the search for new therapeutic targets to combat obesity.

General Pathogenesis of Obesity with Emphasis on Inflammation and Metabolic Changes

The development of the pathological condition in obesity is based on two factors: The release of fatty acids from adipocytes and the increase in the expression of adipokines which are the cytokines and hormones secreted by adipocytes. Adipocytes are endocrine cells that produce a large number of different hormones and cytokines and also function as energy "stores", where energy is stored in the form of triglycerides in the lipid droplets in the cytoplasm (Fasshauer and Bliiher, 2015).

With an excess of nutrient intake, hyperplasia and hypertrophy of adipocytes of white adipose tissue occurs, which is the primary source of the development of a pathological condition in obesity (Balistreri *et al*., 2010). In the normal state, fatty acids are accumulated in the form of triacyl glycerides, however, with their excessive accumulation, which occurs in obesity, fatty acids are released. This process is reinforced by increased lipolysis caused by the dominant sympathetic state in obesity (Redinger, 2007). The released fatty acids cause lip toxicity, due to the resulting oxidative stress, which affects the functioning of various tissues and organs (Evans *et al*., 2004). Increased lip toxicity also leads to impaired functioning of insulin receptors, which subsequently leads to the development of an insulin resistance state and causes hyperglycemia with compensated hepatic gluconeogenesis. During enhanced gluconeogenesis, hepatic glucose production increases, which further exacerbates hyperglycemia (Redinger, 2007). Additionally, fatty acids reduce the uptake of glucose in the muscles, which also contributes to increased hyperglycemia. As a result of lipotoxicity, insulin secretion by pancreatic β -cells decreases, which further leads to β-cells dysfunction (Redinger, 2007).

Adipocytes collectively constitute a large endocrine network that continuously interacts with other tissues of the body through the secretion of hormones such as Lectins, adiponectin, and visfatin. Together with insulin, these hormones are responsible for regulating the amount of fat mass in the body (Matsuzawa *et al*., 2004). In addition to hormones, adipokines include inflammatory cytokines: Tumor Necrosis Factor (TNF-a), Interleukin 1 (IL-1), and Interleukin 6 (IL-6), which are directly involved in the development of the inflammatory response in obesity (Lafontan, 2005). Initially, mild inflammation is caused directly by an excess of nutrients, which leads to the activation of signaling pathways

involving protein kinase R, Nuclear Factor κB (NF-κB), and c-Jun N-terminal Kinase (JNK) (Solinas and Karin, 2010). Developing inflammation leads to increased production of the above-mentioned inflammatory adipokines, which are released from visceral fat into the bloodstream and enter other tissues and organs, affecting them. It has been noted that TNF- α secretion increases in proportion to the increase in body fat mass and increases inflammation in the liver, mesentery, pancreas, and intestines (Redinger, 2007). Adipokines secreted by adipocytes bind to macrophages and recruit them to the site of inflammation (Weisberg *et al*., 2003). Additionally, this is also facilitated by the adipose tissue's own macrophages, which also actively produce inflammatory cytokines. The second reason for the attraction of macrophages to white adipose tissue is the death of adipocytes caused by their increased hypertrophy. Finally, the previously identified free fatty acids released during adipocyte death act as Damage-Associated Molecular Patterns (DAMPs), acting as ligands for the Toll-Like Receptor4 (TLR4) receptor, which enhances inflammation (Kolb *et al*., 2016). In addition, increased inflammation is facilitated by an increase in the production of leptin, which has an inflammatory effect, and a decrease in the production of adiponectin, which is characterized by an anti-inflammatory effect (Kolb *et al*., 2016). In addition to macrophages, a number of other immune cells, such as CD8+ T-lymphocytes, CD4+ T-lymphocytes of the 1st type (Th1), and natural killer cells, are involved in the inflammatory response in obesity (Khan *et al*., 2021).

In addition to being directly involved in the development of the inflammatory response, visceral adipokines contribute to the development of hyperglycemia: Firstly, by directly damaging pancreatic β-cells during inflammation, which leads to a decrease in insulin secretion; secondly, the adipokine-activated transcription factor NF-KB, which plays the role of one of the central initiators of inflammation, dephosphorylates the Insulin Receptor Substrate 2 (IRS-2) protein, which has an inhibitory effect on the Glucose Transporter type4 (GLUT4), which leads to the development of insulin resistance in cells (Redinger, 2007). Also, inflammatory cytokines are able to inhibit lipolysis by inhibiting the activity of lipoprotein lipase, thus increasing the concentration of triacylglycerol (Redinger, 2007). The increased secretion of renin and angiotensin observed in obesity leads to the development of a hypertension state (Engeli *et al*., 2003). The narrowing of the vessel's lumen, together with the accumulation of lipid molecules in the plasma and the development of an inflammatory reaction, dramatically increases the risk of developing atherosclerosis, which is often detected in overweight people (Lau *et al*., 2005).

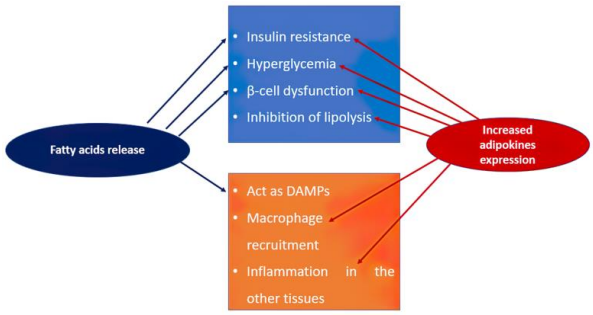

Fig. 1: Dual effect of fatty acids and adipokines on the pathogenesis of obesity

Thus, both fatty acids and adipokines have a dual effect on the pathogenesis of obesity, causing the development of inflammation on the one hand and contributing to changes in lipid and carbohydrate metabolism, which is shown in Fig. 1.

Mitochondrial Functions the Role of Mitochondrial Dysfunction in The Development of Inflammation

Mitochondria are important cellular organelles necessary for the proper functioning of cells. There is a theory according to which it is believed that mitochondria originated from alpha-proteobacteria during a long symbiosis between these types of bacteria and eukaryotic cells (Lane and Martin, 2010). The proof of this is their structure: Like alpha-proteobacteria, mitochondria are covered with two structurally and functionally different membranes: An out-er membrane and an inner membrane, between which there is a medium called the inter-membrane space, the inner membrane surrounds the mitochondrial matrix, which contains autonomous circular DNA. Mammalian mitochondria contain more than one and a half thousand proteins, but only 13 of them are encoded directly in mitochondrial DNA, while the rest are encoded in nuclear DNA and, after transcription and translation processes, are imported into the mitochondrial compartment intended for them, after which they can be assembled into macromolecular complexes, consisting of individual protein subunits (Nunnari and Suomalainen, 2012).

The main function of mitochondria is gaining energy. In these organelles, through the process of oxidative phosphorylation, molecular energy carriers are formed, which are the Adenosine Triphosphate (ATP) molecules. The energy released during the breakdown of which is subsequently used to meet cellular needs. In the mitochondrial matrix, as a result of the tricabronic acid cycle, reduced electron carriers, Hydro Nicotinamide Adenine Dinucleotide (NADH), and Dihydroflavine-Adenine Dinucleotide (FADH2) molecules are formed as reaction products, which then transfer electrons to the

electron transport chain located on the inner mitochondrial membrane. The electron transport chain consists of electron carriers, as well as respiratory complexes are the large protein structures consisting of several (in some cases) several dozen subunits that carry out the transfer of protons formed during redox reactions from the matrix to the intermembrane space, which releases energy for the synthesis of ATP from Adenosine Diphosphate (ADP) (Nunnari and Suomalainen, 2012).

However, in addition to energy production, mitochondria also perform a number of other important functions. During oxidative phosphorylation, Reactive Oxygen Species (ROS) are generated as side products of the reaction in respiratory complexes I and III, representing various forms of oxygen radicals and hydrogen peroxide (Murphy, 2009). The normal function of ROS is to influence the signaling pathways of cellular homeostasis, which are necessary for the implementation of the processes of cell proliferation and differentiation, as well as the adaptive response to stress conditions, such as the occurrence of hypoxia (Hamanaka and Chandel, 2010). Thus, in mouse models of aging, it was found that hematopoietic stem cells were highly sensitive to signaling involving ROS and changes in the redox balance of the cell (Ito *et al*., 2004). In addition to cellular respiration, mitochondria are also involved in other metabolic processes: Fatty acid metabolism, synthesis of cofactors of various enzymes, regulation of the level of various amino acids in the cell, and synthesis of heme, the central component of hemoglobin (Nunnari and Suomalainen, 2012). Another important function of mitochondria is the regulation of calcium homeostasis, an important cell signaling molecule, by modulating calcium fluxes from the endoplasmic reticulum and plasma membrane (De Stefani *et al*., 2011). In neurons, this mitochondrial function is required to control the production of neurotransmitters, as well as neurogenesis and neuronal plasticity (Waagepetersen *et al*., 2001). It should also be noted that some mitochondrial proteins (for example, cytochrome C) are involved in the initiation of apoptosis via the intrinsic pathway, thus making mitochondria one of the regulators of cell death (Polster and Fiskum, 2004).

Mitochondria are not static cellular structures; they are subject to the processes of mitochondrial dynamics that are necessary to maintain a functionally stable pool of mitochondria. Mitochondrial dysfunctions are dangerous in that the cellular processes subordinate to their action are disturbed, however, if dysfunctions of individual mitochondria are also accompanied by a disruption of the processes of mitochondrial dynamics, this leads to a larger-scale negative impact on cellular homeostasis, since the disruption of the one mitochondria work extends to the work of most mitochondria in the cell. The processes of mitochondrial dynamics are subdivided into the processes of fusion, fission and transport of mitochondria, as well as mitophagy (Nunnari and Suomalainen, 2012). The processes of mitochondrial dynamics affect the overall shape, arrangement, and interconnection of mitochondria within a cell. The fusion of mitochondria is necessary to restore the functioning of damaged mitochondria: When dysfunctional and normally functioning mitochondria merge, the newly formed mitochondrion is functional because of the redistribution of its components of the intermembrane space and matrix (Chen *et al*., 2010). The division of mitochondria is necessary to maintain their numerical composition and facilitate the transfer between cell compartments (Verstreken *et al*., 2005). Mitochondrial transport ensures the transfer of mitochondria to cell compartments that most urgently need an influx of ATP energy (Wang and Schwarz, 2009). For example, in neurons that have a polarized structure, the largest number of mitochondria is concentrated in presynaptic terminals, since the transmission of a nerve impulse is a highly energy-consuming process (Verstreken *et al*., 2005). Mitophagy is designed to remove damaged mitochondria that can no longer be repaired by fusion. Mitophagy not only maintains a high concentration of healthy mitochondria but also provides cellular protection since damaged mitochondria can pose a threat as a source of inflammation and initiation of cell death. Mitophagy proceeds by sequestration (separation from the cytosol) of the mitochondria selected for destruction with the formation of an autophagosome and the subsequent fusion of the resulting structure with the lysosome, where the final degradation of the mitochondrion occurs (Youle and Narendra, 2011).

Mitochondria are complexly organized structures that perform numerous functions and in many respects, this complexity makes mitochondria highly vulnerable organelles. Let us consider in more detail the causes of mitochondrial dysfunctions. One of the causes of mitochondrial dysfunction is the occurrence of mutations in mitochondrial DNA. Although only 13 of the more than 1500 mitochondrial proteins are encoded in the mitochondrial DNA itself, these proteins are responsible for oxidative phosphorylation and their mutations can disrupt the overall process of ATP production. The rate of mutagenesis in mitochondrial DNA is 10-20 times higher than in nuclear DNA, which makes it highly vulnerable (Annesley and Fisher, 2019). Another cause of mitochondrial dysfunctions is the impaired transport and assembly of mitochondrial proteins (Mackenzie and Payne, 2007). Since most of the mitochondrial proteins are encoded in the nucleus, a clear regulation of the delivery system from the nucleus to the mitochondria is necessary, which can be disturbed. Also, a vulnerable point is the assembly of respiratory complexes of the respiratory chain, consisting of several subunits, some of which can be encoded in the

mitochondria itself and some in the nucleus. A disruption of the assembly process also leads to disruption of the electron transport chain. Mutations or inhibition of the main proteins of mitochondrial dynamics: (Mitochondrial Fission Factor (MFF), Dynamin-Related Protein (DRPL)) mitochondrial division, (Mitofusin-1 (MFN1), Mitofusin-2 (MFN2)) Mitochondrial fusion, (Miro) Mitochondrial Transport, (PTEN-Induced Kinase 1(Pink1), Parkin) mitophagy-leads complex disorders in the functioning of mitochondria, spreading immediately to the entire cell (Nunnari and Suomalainen, 2012). Disruption of work can affect each function performed by the mitochondria. If oxidative phosphorylation is disturbed, the cell switches to energy-saving mode with a slowdown in the study of many processes and a metabolic shift towards glycolysis. In the case of a severe lack of energy, cell death occurs; in the interruption of mitochondria-mediated apoptosis the cell cycle is disrupted, which increases the risk of accumulation of harmful mutations by the cell and the development of tumors. Disruption of the ROS production represents their excessive production due to a malfunction of the electron transport chain leads to the development of oxidative stress and subsequent inflammatory response. In this review, there is a focus in more detail on mitochondrial dysfunction associated with ROS production. As described above, ROS is normally a signaling molecule that performs important functions in the pathways of cellular homeostasis; however, in a number of diseases, the production of ROS, which is usually a by-product of electron transfer reactions during oxidative phosphorylation, is greatly increased. ROS are dangerous because they can damage biological macromolecules: Proteins, lipids, and nucleic acids and, accordingly, organelles and other cellular structures (for example, the cytoplasmic membrane) of which they are composed (Mittal *et al*., 2014). Being released in large quantities, ROS themselves become sources of mitochondrial dysfunction, causing damage to the organelles that produced them, thereby exacerbating the situation. Damaged mitochondria are sources of mitochondrial DAMPs, which, when they enter the extracellular space, initiate an inflammatory response by binding to immune cells (Missiroli *et al*., 2020). In addition to the fact that ROS cause the formation of mitochondrial antigens, which lead to the induction of inflammation, they can independently initiate an inflammatory response through the activation of transcription factors HIF-1α and NF-kB, which lead to an increase in the expression of pro-inflammatory cytokines (Missiroli *et al*., 2020). The role of mitochondrial ROS in the development of inflammation has been shown for a number of oncological, neurological, and autoimmune diseases (Missiroli *et al*., 2020; Tian *et al*., 2017; Volpe *et al*., 2018).

Methodology

To achieve the aims of this review: Creating a new pathological model of obesity and proposing therapeutic strategies based on it, a large-scale analysis of the scientific literature was carried out.

The first step was to conduct a search to select the most relevant sources using databases: Medline (PubMed), Cochrane Library, and Google Scholar. The search was carried out using keywords on this topic: “Mitochondrial dysfunction", "obesity", "oxidative stress", "carbohydrate metabolism", "lipid metabolism", "fatty acids", "adipokines", "ETC" etc. Multiple related search terms were used for a single search query. The search results yielded more than 100 articles.

The second step was a careful selection of the most suitable sources from those already found. The selection principle was the possibility of collecting the greatest amount of information about a certain pathological fact in obesity, for example, “changes in energy consumption in obesity” or “changes in the antioxidant state of adipocytes in obesity.” Thus, about 40 articles were re-selected and divided into groups according to the factors in the pathogenesis of obesity that were described in them.

The third step was the direct construction of a dynamic model of the development of the pathogenesis of obesity, in which mitochondrial dysfunction and oxidative stress played a central role. This model was built based on an analysis of the facts obtained during the selection of articles in the second step.

The fourth step was to propose treatment strategies for obesity based on the developed model associated with the development of mitochondrial dysfunction. For this purpose, an additional search and selection was carried out aimed at finding the most promising compounds.

Results

Model of Inflammatory Pathogenesis of Obesity Based on Mitochondrial Dysfunction

Increased nutrient intake leads to an excess content of energy substrates: Lipids and glucose, as a result of which the study of the tricarboxylic acid cycle is enhanced, which leads to excessive production of electron carriers NADH and FADH2 (McMurray *et al*., 2016; Manna and Jain, 2015). In this case, the number of transferred electrons in the electron transport chain increases, which inevitably leads to electron leakage in complex III with the formation of an increasing amount of ROS (Manna and Jain, 2015). ROS in high concentration damages highly sensitive mitochondrial DNA, which leads to the appearance of mutations in the subunits of the respiratory centers, the accumulation of which can lead to malfunction of the electron transport chain and, as a result, to mitochondrial dysfunction.

Mitochondrial dysfunction can also be caused by direct damage to mitochondrial enzymes involved in the process of oxidative phosphorylation, which will eventually lead to a metabolic shift in energy production towards glycolysis. Damage to membrane mitochondrial proteins with the participation of ROS leads to the formation of DAMPs with subsequent activation of inflammation. In addition to a direct negative effect on mitochondria, leading to their dysfunction and destruction, increased ROS formation causes changes in cellular metabolism (Pennathur and Heinecke, 2004): Glucose begins to actively participate in the polyol pathway, fructose-6-phosphate is used in the reactions of the hexosamine pathway, dihydroxyacetone phosphate is transformed into diacyl glycol, which activates the protein kinase C signaling pathway, triose phosphates are converted to methylglyoxal, which is the main source of advanced glycation end products. Activation of these pathways leads to increased oxidative stress through the formation of free radicals and disruption of the antioxidant defense system. Thus, upon activation of the polyol pathway, the concentration of sorbitol increases, which leads to the expression of several genes that are activated under stress conditions (Evans *et al*., 2002). Activation of the hexosamine pathway, during which glucosamine-6-phosphate is formed, leads to inhibition of the activity of thioredoxin, which is one of the important components of the cell's antioxidant defense system (Diaz-Meco and Moscat, 2012).

Decreased activity of antioxidant enzymes has also been shown in several animal models of obesity (Furukawa *et al*., 2017). Protein kinase C and advanced glycation end products cause increased production of ROS and Reactive Nitrogen Species (RNS) through the activation of NADPH oxidase, an enzyme whose reaction product is the superoxide radical, and NF-kB, a transcription factor that activates the transcription of adhesion molecules (E-selectin, endothelin-1), pro-inflammatory cytokines (TNF-a, IL-6) and inducible NO Synthase (iNOS), which catalyzes the formation of NO, a strong inflammatory factor, as well as a number of microRNAs involved in the development of the inflammatory response (Diaz-Meco and Moscat, 2012). A high content of organic metabolites: Glucose, lipids, free fatty acids and a high concentration of ROS leads to the fact that macromolecules become convenient targets for oxidative damage involving ROS, which leads to the formation of new radicals and the accumulation of by-products of the oxidative reaction, which can be toxic to cells and increase inflammation (Furukawa *et al*., 2017). Thus, in patients with obesity, an increased concentration of 4-hydroxynonenal, a toxic aldehyde formed as a result of lipid peroxidation, was found (Russell *et al*., 2003).

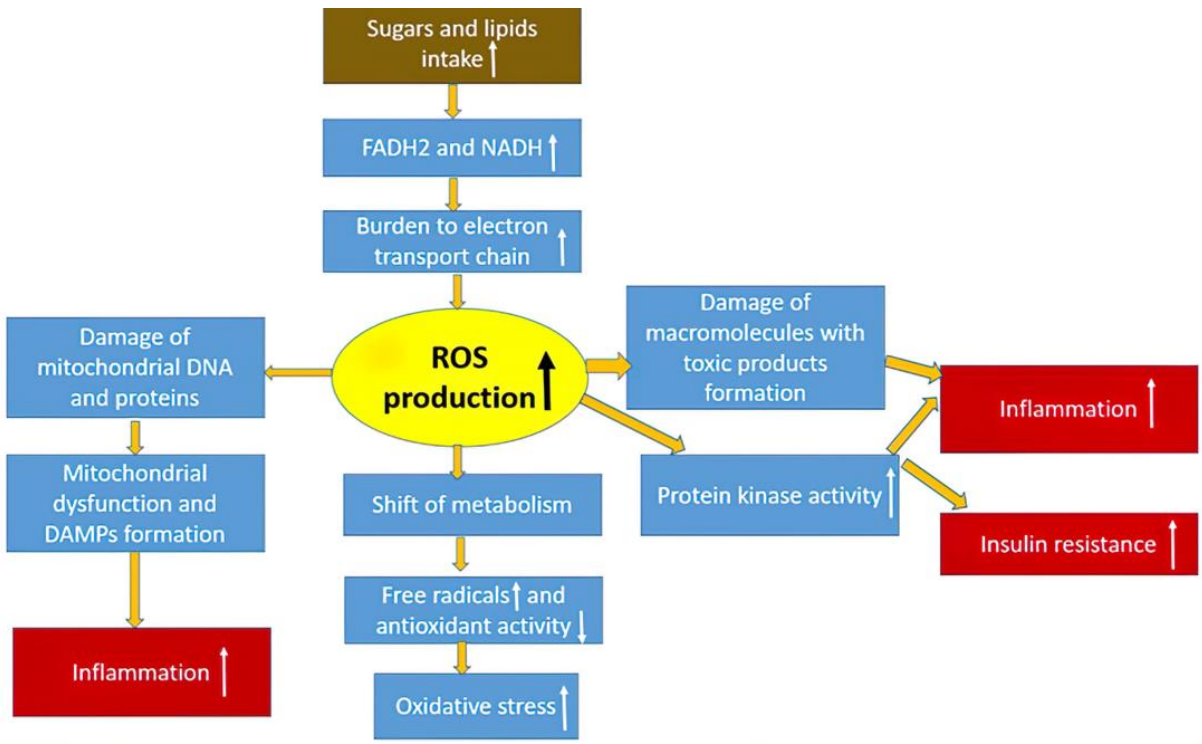

Fig. 2: The diagram of the inflammatory pathogenesis of obesity involving mitochondria

In addition to reactions to increased oxidative stress and the development of an inflammatory response, ROS can trigger reactions leading to an increase in cell resistance to insulin. ROS activate protein kinases: Mitogen-Activated Protein Kinase (MAPK), p38MAPK, mammalian Target of Rapamycin (mTOR), Protein Kinase C (PKC), which are able to change the affinity of insulin to their receptor by phosphorylation of serine residues on the insulin receptor (Monteiro and Azevedo, 2010). Also, these kinases have an enhancing effect on the regulation of the expression of pro-inflammatory cytokines by activating Activating Protein-1(AP-1) and NF-kB (Baud and Karin, 2001). Ceramide, which is formed as a result of changes in the dominant metabolic pathways, is also involved in increasing insulin resistance through the activation of protein phosphatase 2A; in addition, its secondary metabolites can cause increased inflammation (Wymann and Schneiter, 2008). Thus, ROS formed during excessive intake of energy substrates causes mitochondrial dysfunction, the development of inflammation, and an increase in insulin resistance. ROS creates a self-reinforcing system for their generation, which leads to the establishment of a chronic inflammatory response. A diagram of the inflammatory pathogenesis of obesity involving mitochondria is shown in Fig. 2.

Ways to Restore Mitochondrial Function in Obesity

Restoration of adequate mitochondrial performance in adipose tissue cells, as well as in cells of other tissues where there is a decrease in mitochondrial function, can become a definite trigger for ineffective obesity therapy (Marcovina *et al*., 2013). Here the three most significant factors highlighted that contribute to the restoration of mitochondrial functions in patients with obesity: Taking pharmaceuticals that are analogs of natural cellular components that ensure the maintenance of mitochondrial function; normalization of nutrition in order to reduce the energy load on mitochondria and the gradual introduction of moderate aerobic exercise into the lifestyle of patients.

Among the pharmaceutical compounds for the treatment of obesity, the use of antioxidants, or compounds that increase their activity in the cell, seems promising (Tun *et al*., 2020). Indeed, with the development of an inflammatory response, the concentration of ROS sharply increases, while it is noted that the natural antioxidant system can be inhibited, so the introduction of new components of antioxidant protection can be an excellent help in neutralizing the resulting ROS. One possible option could be the use of alpha-lipoic acid, which is a powerful antioxidant and has been shown to have clinical efficacy in the treatment of complications caused by diabetes mellitus (Shay *et al*., 2009). In addition, alpha-lipoic acid reduces the level of ceramides, which contributes to an increase in the function of the electron transport chain and participates in the restoration of glutathione, an intracellular component of antioxidant defense (Monette *et al*., 2011). Another promising compound is L-carnitine, whose function is to transport fatty acids into the mitochondrial matrix, where fatty acids undergo β -oxidation (Marcovina *et al*., 2013).

From the general pathogenesis of obesity, it is known that free fatty acids are one of the main triggers of the inflammatory response in obesity, so increasing their oxidation will help remove these harmful metabolites in the context of obesity. L-carnitine therapy is already used in a number of diseases associated with mitochondrial dysfunction: Diabetes, renal failure, sepsis, and cardiomyopathy (Marcovina *et al*., 2013). Another therapy option can be the intake of coenzyme CoQ 10 (ubiquinone), which is a direct participant in the electron transport chain in mitochondria (Littarru and Tiano, 2010). The main component that suffers from mitochondrial dysfunction is the electron transport chain, so the introduction of additional "working units" can help restore the work of oxidative phosphorylation. CoQ 10 has been shown to be effective in reducing the progression of neurodegenerative diseases: Parkinson's disease and Alzheimer's disease (Littarru and Tiano, 2010).

An excess amount of energy substrates supplied with food creates an additional load on the work of mitochondria, which affects the accelerated leakage of electrons from the electron transport chain and increased formation of ROS. Reducing the intake of increased amounts of lipids and sugars can normalize the process of oxidative phosphorylation, which will reduce the production of ROS and the subsequent inflammatory response in addition to preventing further accumulation of adipose tissue in the body. Moderate aerobic exercise, along with the introduction of a diet, is one of the main non-drug measures to combat obesity. In a study (Fritzen *et al*., 2020), it was shown that aerobic exercise leads to an increase in the activity of the protein complexes of the electron transport chain, both in young and elderly mice. In a study in the C57BL/6 mouse model, it was found that even despite a high-fat diet, exercise led to an increase in mitochondrial number and size and reduced diet-induced obesity and hyperglycemia (Heo *et al*., 2021). Thus, aerobic exercise can improve the function of mitochondria, and increase their number and size, which will help restore the normal state of energy metabolism and reduce the development of hyperglycemia and inflammation.

Discussion

Understanding the pathways of obesity pathogenesis involving mitochondria opens up new possibilities for combating this disease. Based on the study results, a new pathological model of obesity was developed. It is based

on a number of other studies on this topic, which, however, describe individual pathological conditions that are not linked into a united model of pathogenesis, for example (Russell *et al*., 2003) lipid peroxidation in obesity; (Furukawa *et al*., 2017) decreased antioxidant activity in obesity. However, a number of important questions and challenges still remain open, the answers to which will provide more accurate therapeutic options for the treatment of obesity. First, what concentration of incoming nutrients is critical for the development of mitochondrial dysfunction? A related and still unresolved question is, what is the amount of ROS that is sufficient to cause oxidative stress? Second, what molecular targets are damaged by ROS the most during the development of inflammation and, accordingly, act as the main DAMPs in the initiation of inflammation? Thirdly, it is not completely clear what energy expenditure is optimal for training for people with different degrees of obesity, based on the effectiveness of exercise in restoring mitochondrial function. More research is also needed on the impact of dietary calories on mitochondrial function. With regard to drug assistance, it is important to search for new compounds that have a beneficial effect on mitochondrial function.

Conclusion

An important role in the pathogenesis of obesity is performed by the inflammatory response, the key initiators of which are free fatty acids and adipokines, which, in addition to directly triggering inflammatory cascades, also cause hyperglycemia. However, the pathogenesis of obesity is more complex and can develop through the activation of other factors, one of which is a disruption of mitochondrial function. The novelty of this study lies in establishing the causes of the development of mitochondrial dysfunction, as well as its consequences for the development of obesity. This disorder, caused by an excess of energy substrates, leads to the growth of reactive oxygen species, which trigger reactions of inflammation, cell death, and hyperglycemia. The intake of antioxidants and related compounds targeting mitochondria, reduced intake of fats and sugars and moderate aerobic exercise can normalize mitochondrial function in obese patients. In addition, the results of this study may inspire other researchers to study the use of other promising compounds that restore mitochondrial function in the treatment of obesity.

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Author's Contributions

Alexander Blagov and Varvara Orekhova: Data analysis, original drafted preparation, final approval.

Vasily Sukhorukov, Aicksandra Meinichenko and Alexander Orekhov: Manuscript designed development, reviewed and edited, final approval.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and that no ethical issues are involved.

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