REVIEW

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Mechanism of oxidative stress in obesity

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ABSTRACT

Reactive oxygen species (ROS) levels are strongly linked to obesity and related diseases, particularly insulin resistance and type 2 diabetes. ROS, on the other hand, are thought to be important in intracellular signaling, which may be required for insulin sensitivity. Many theories have been developed to explain this apparent paradox, which has helped us understand this important small molecule better. While many intracellular ROS production sites have been identified, mitochondrial-generated ROS remains a major contributor in most cell types. Some factors described in this review influence mitochondrial ROS generation. Furthermore, this review has demonstrated the need for a new sensitive approach to quantifying ROS.

Keywords: oxidative stress, mechanism, obesity.
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INTRODUCTION

Obesity is a complex disease that involves an excessive amount of body fat. It is not just a cosmetic issue, but a medical matter that increases the risk of other diseases such as heart attack, diabetes, high blood pressure, and certain cancers. There are many reasons why some people have difficulty losing weight. Usually, obesity is caused by innate factors, physiological and environmental aspects combined with a bad diet, low physical activity, and exercise choices.

Obesity is commonly caused by consuming more calories, especially those in fatty and sugary foods than you burn through physical activities. The body stores excess energy as fat. It is an increasingly common problem for many people in modern life because most of them like to eat excessive amounts of high-calorie foods and spend much time sitting in a chair, on the couch, or in the car.[1]

Obesity is one of the most common health problems among children and adolescents in developed and developing countries. Besides, it is the main causative factor in various diseases, such as dyslipidemia, atherosclerosis, cardiovascular, and others. It can also increase the risk of early disease and death in later days and trigger public health problems. Oxidative stress results from an imbalance among the production of reactive oxygen species (ROS), such as superoxide (O2) and hydroxyl (OH^-) radicals, and antioxidant defenses, leading to oxidative damage to lipids, proteins, and DNA. This may be the mechanism underlying these complications related to obesity. The human body has developed several mechanisms to protect biomolecules from the damaging effects of ROS. They are antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GSSG-R), and glutathione peroxidase (GSH-Px), as well as water and lipid-soluble antioxidants, such as GSH, ascorbate (vitamin C), -tocopherol (vitamin E) and -carotene. They function to detoxify ROS, convert superoxide radicals (O2) to H_2O_2, and metabolize peroxide organic molecules. Glutathione protects body organs against ROS oxidative stress, either directly as an antioxidant or indirectly by maintaining other cellular antioxidants in a functional state.[1,2]

Oxidative stress is a disruption in the balance of ROS production and antioxidant defense. At the molecular level, ROS mainly arise from the mitochondria. Electron transfer via ETC produces superoxide anions as a by-product, with complexes I and III representing the sources of ROS. Under certain situations, complex II and other sources of cellular ROS may contribute to the overall assemblage. Superoxide is the ROS species that reacts with Fe-containing proteins to produce H_2O_2. The accumulation in cells contributes directly to the metabolic imbalance linking excessive nutritional stress and resistance. However, ROS also includes many chemical entities, including nitric oxide, peroxynitrite, hypochlorous acid, singlet oxygen, and hydroxyl radicals. Therefore, broader biological impacts of ROS come from multiple cells and tissue microenvironments, dividing physiological and pathological effects.[3]

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Metabolic syndrome is triggered by the interaction of the gut microbiota, diet, and genetics. Diet is currently a strategy for preventing and treating metabolic syndrome. Diet affects genes involved in metabolic functions. Weight loss up to 5-10% through diet and exercise improves metabolic syndromes. Puberty changes such as organ maturation, brain plasticity, and changes in behavior and social environment have health implications as puberty goes to adulthood. Health interventions should be implemented during adolescence to prevent more health complications during adulthood. Information about metabolic syndrome and nutrition in obese adolescents is expected to increase their awareness to prevent the development of metabolic syndrome or severe complications.[4]

Prolonged oxidative stress can directly affect metabolism, including the enzymes' activities in the tricarboxylic acid (TCA) and electron transport chain (ETC) cycles. The TCA cycle of the aconitase enzyme catalyzes the interconversion of citrate and isocitrate to regulate intermediates for lipid synthesis and adenosine triphosphate (ATP) production.[5] Citrate is the last common metabolite in the acetyl-CoA oxidation pathway and is exported for fatty acid synthesis in the cytoplasm. Superoxide inhibits aconitase leading to the transfer of acetyl-CoA away from mitochondrial oxidative phosphorylation system (OXPHOS) toward fat storage. This feedback loop may be part of an antioxidant defense mechanism adapting prolonged mitochondrial superoxide production. The transfer of acetyl-CoA can slow down the delivery of electron carriers such as nicotinamide adenine dinucleotide (NADH) to the respiratory chain, thereby decreasing the production of ROS.[6] Oxidative stress also influences the inhibition of pyruvate dehydrogenase kinase 2 (PDK2) of the pyruvate dehydrogenase complex (PDC) and fat metabolism. ROS oxidize critical cysteine residues, inactivate PDK2, and support acetyl-CoA synthesis from glucose-derived pyruvate. Therefore, increased mitochondrial superoxide and H_2O_2 divert citrate from the TCA cycle to the cytoplasm as triglycerides during nutrient overload. These studies show persistent nutritional stress impairs the physiological behavior of important metabolic enzymes required for balanced ATP generation and consumption.[7]

Concept and cause of obesity

a. High Fat Diet

A high-fat diet can stimulate voluntary fat intake. The high palatability of a high-fat diet may cause overeating and a higher energy density of fat. Rich diets have been shown to increase energy intake due to possibly 'passive overeating'. On the other hand, obese-prone subjects seem to have more difficulty adjusting their fat oxidation when switching to a high fat intake, and they prefer fat storage. Post-obese women fail to properly increase their fat oxidation after a 3-day adaptation period on a 50% fat diet, while control subjects can successfully adapt.[8]

b. Etiology of obesity

Energy balance can only be achieved if there is a balance between energy intake and expenditure. According to the first law of thermodynamics (i.e. energy can neither be created nor destroyed), excess energy is stored as triacylglycerol in adipose tissue. The main function of adipocytes is to store energy when there are excessive calories and to mobilize energy from this triacylglycerol reservoir when energy requirements exceed intake (i.e. during dieting and starvation).[9]

c. Adipose Tissue

Adipose tissue is now recognized as a very important and active endocrine organ. It is well known that adipocytes (or fat cells) greatly influence the storage and release of energy throughout the human body. Recently, the endocrine function of adipose tissue has been discovered. Besides adipocytes, adipose tissue contains many other cells which produce certain hormones in response to signals from other body organs. Through the action of these hormones, adipose tissue regulates glucose, cholesterol, and sex hormone metabolism.[9-12]

Mechanism of Oxidative Stress in Obesity

a. Leptin

Leptin is a hormone. It is a chemical messenger that helps different parts of the body work together. Leptin sends signals to the brain that helps to feel full and less interested in consuming more food. It is commonly called the satiety hormone (Satiety means "hunger has been satisfied").[13]

While the role of leptin has been classically described in the regulation of appetite, neuroendocrine function and energy homeostasis seem to influence several other physiological processes. They include metabolism, endocrine regulation, and immune function, with other possible functions still waiting for characterization. Leptin abnormalities are associated with various metabolic syndromes, especially obesity. The study of leptin physiology has contributed to our understanding of energy homeostasis and is likely to impact the development of effective treatments and solutions to the growing obesity epidemic. Total body fat mass index (BMI), metabolic hormones, and sex are some factors that have the greatest effect on circulating plasma leptin concentrations.[2,13]

The main site of leptin's action is in the brain, specifically in the brainstem and hypothalamus. The actions in the brainstem cover the solitary tract and the ventral tegmental area. Leptin works to modulate satiety and control reward and aversion. Hypothalamus, lateral hypothalamic regions and ventromedial, dorsomedial, ventral premaxillary, and arcuate (ARC) nuclei are the principal sites of leptin's actions. Activation of those areas causes different changes, including in the thyroid, gonads, adrenocorticotropic hormone-cortisol growth hormone axes, and in whole-brain cognition, emotion, memory, and structure.[14]

b. Tumor Necrosis Factor Alpha (TNF-α)

Tumor necrosis factor alpha (TNF-α) is a cytokine that has a pleiotropic effect on various types of cells. It has

been identified as a regulator of the inflammatory response. It is also known for the pathogenesis of several inflammatory and autoimmune diseases. Structurally, TNF- α is a homotrimeric protein consisting of 157 amino acids, mainly produced by activated macrophages, T lymphocytes, and natural killer cells. Functionally it triggers a range of various inflammatory molecules, including cytokines and other chemokines. TNF- α exists in a soluble and transmembrane form. Transmembrane TNF-α (tmTNF-α) is the precursor form synthesized and required for processing by TNF-α-converting enzyme (TACE), and a membrane-bound disintegrin metalloproteinase for release as soluble TNF-α (sTNF-α).[15] In general, TNF binds to its receptors, particularly TNF-receptor 1 (TNFR1) and TNFR2, and then transmits molecular signals for biological functions such as inflammation and cell death. TNFR1 is activated by sTNF-α and tmTNF-α to process the death domain (DD) that interacts with the TNFR1-associated death domain adapter protein (TRADD).[2]

c. Interleukin 6 (IL-6)

It is a group of related proteins made by leukocytes (white blood cells) and others in the body. Interleukin regulates the immune response. It can be made in the laboratory and is usually a biological response modifier to boost the immune system in cancer therapy. Interleukin is a type of cytokine. Therefore, it aims to modulate growth, differentiation, and activation during inflammatory and immune responses. Interleukin consist of a large group of proteins that can elicit multiple reactions in cells and tissues by binding to high-affinity receptors on the cell surface. It has paracrine and autocrine functions. It is also used in animal studies to investigate aspects related to clinical medicine.[16,17]

d. Angiotensinogen /PAI-1

Angiotensinogen is a component of the renin-angiotensin system (RAS). It is a hormone system that regulates blood pressure and fluid balance. It is also known as a renin substrate and is a non-inhibitory member of the serine proteinase inhibitor family (MEROPS inhibitor family I4, clan ID, MEOPS identifier I04.953). Angiotensinogen is catalytically broken down by renin to produce angiotensin I to respond to blood pressure drops. The angiotensin-converting enzyme (ACE) then secretes dipeptides to produce angiotensin II, a physiologically active peptide that regulates body fluids' volume and mineral balance.[18]

e. Adiponectin

Adiponectin is an adipokine hormone and protein that influences some metabolic processes and is primarily known for its insulin-sensitizing and anti-inflammatory effects. The adipose tissue (body fat) generates adiponectin, although other tissues also produce it. Hormones are chemicals that coordinate different bodily functions by carrying messages through the blood to other organs, muscles, and tissues. These signals tell the body what to do and when to do it. Adipokines (also called adipocytokines) are adipose tissue hormones that functionally influence energy and metabolic processes. Metabolic processes (metabolism) are the many chemical reactions in the body that convert food (calories) into energy and transport that energy to all of the cells.[2,19]

f. Adepsin

Adipokines (or adipocytokines) are a group of more than 600 bioactive molecules made from adipose tissue that acts as paracrine and endocrine hormones. Adipokines maintain various processes such as appetite and satiety, energy expenditure activity, endothelial function, blood pressure, hemostasis, adipogenesis, insulin sensitivity, energy metabolism in insulin-sensitive tissues, fat distribution, and insulin secretion in pancreatic cells. Adipsin also referred to as complement factor D, is one of the first adipokines that describe adipokines. Adipsin is a member of the serine protease family with a 28-kilo Dalton protein found in 3T3 adipocytes. Adipsin maintains adipose tissue homeostasis and increases insulin secretion in response to glucose. Also, it catalyzes the production of C3a (the active form of component 3, C3) by controlling the alternative complement pathway, leading to increased insulin secretion from the pancreas.[2,20]

g. Resistin

Resistin is also described as an adipocyte-specific hormone. It has an important link between obesity, insulin resistance, and diabetes. Although its expression was defined in adipocytes, significant levels of resistin expression in humans are mainly found in mononuclear leukocytes, macrophages, spleen, and bone marrow cells. Increasing evidence indicates that resistin plays a regulatory role in addition to its role in insulin resistance and diabetes in many biological processes: atherosclerosis and cardiovascular disease (CVD), non-alcoholic fatty liver disease, autoimmune disease, malignancies, asthma, inflammatory bowel disease, and chronic kidney disease. Because CVD accounts for a significant amount of morbidity and mortality in patients with and without diabetes, it is important to understand the role of adipokines, such as resistin in the cardiovascular system. Evidence shows that resistin is involved in the pathological processes which trigger CVD, including inflammation, endothelial dysfunction, thrombosis, angiogenesis, and muscle cell dysfunction.[21]

h. Other Adipokines

The mechanism of free radical formation in obesity is explained in the following section:

1. Adipose tissue

   Adipose tissue can be found in some sites throughout the body. White adipose tissue is the most abundant type of fat in humans. It is distributed in subcutaneous fat, visceral fat, and bone marrow fat. Subcutaneous fat is found throughout the body, in the space

between the skin and the muscles underneath. Visceral fat is around organs in the abdominal cavity, such as the liver, intestines, and kidneys, as well as the peritoneum (the serous membrane that lines outside the abdominal organs). White adipose tissue is also there in the bone marrow (spongy tissue present in the middle cavity of bones). Besides, it is also in the pericardium that surrounds the heart or cushions other body parts, such as the soles of the feet, eyeballs, and certain blood vessels.[10,21]

2. Fatty acid oxidation
   Peroxisomes are responsible for beta-oxidation of very long-chain fatty acids (>C20), dicarboxylic fatty acids, 2-methyl branched fatty acids, prostaglandins, leukotrienes, carboxyl side chains of certain xenobiotics, and bile acid intermediates di- and tri-hydroxycoprostanic acid. Mitochondria oxidize long-chain fatty acids (C16-C20) because their abundance is the source of metabolic fuel.[22]
3. Excessive oxygen consumption
   Obesity increases mechanical and metabolic stress on the myocardium, thereby increasing oxygen consumption. One of the negative consequences of increased oxygen consumption is the production of ROS such as superoxide, peroxide radicals, and hydroxy hydrogen due to mitochondrial respiration and the loss of electrons in the transport chain.[23]

Abdominal adipose tissue has more macrophages than others. The proliferation of adipose tissue and chronic obesity leads to premature activation of the inflammatory process, which triggers metabolic syndrome. Increased inflammatory mediators and oxidative stress cause insulin resistance, dyslipidemia, and hypertension. This is indicated by an increase in hsCRP in the metabolic syndrome. Oxidative stress occurs when the balance between pro-oxidants and antioxidants is disrupted. Endogenous and exogenous antioxidants control oxidative stress. Exogenous antioxidants come from vitamins E and C (fruits and vegetables). Therefore, we should eat antioxidant-rich foods more like fruits, vegetables, and nuts.[3,6]

CONCLUSIONS

Overweight adolescents should consume more fish, vegetables, and fruits. There is no difference in dietary profile between overweight adolescents with and without metabolic syndrome. Nutrition knowledge in overweight teenagers must be communicated early to avoid further complications. Increasing the consumption of foods containing unsaturated fats and antioxidants and reducing the consumption of saturated fats are strategies to prevent metabolic syndrome. In obesity, excessive adipose tissue deposition increases adipokine secretion. Besides, fatty acid oxidation and increased oxygen consumption in fats lead to increased mitochondrial respiration, generating superoxide, peroxide radicals, and hydrogen hydroxide. Reducing body fat increases oxidative signaling, and antioxidant activity and leads to obesity. Therefore, antioxidants such as vitamins E, A, and C and flavonoids, along with weight loss through a healthy diet and therapy, can reduce the risk of hypertension-related diseases such as oxidative stress and obesity. There is obesity with metabolic syndrome.

CONFLICT OF INTEREST

All author declares there is no conflict of interest.

AUTHOR CONTRIBUTION

All author had contributed to manuscript writing and agreed for the final version of the manuscript for publication.

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ETHICAL CONSIDERATION

Ethical clearance is not mandatory in review article.

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