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Review Article

Role of adipose tissue in people with obesity and its relationship with the appearance of metabolic diseases

Steven M. Suárez Velastegui[1], Carmen P. Montes Castro[2], Myrna A. Córdova Perugachi[3], Martín I. Rodríguez[3], Gisella G. Riofrio[4], Cristhian A. Coral[5], Carlos A. Chango[1]*, Lizeth A. Navas Balarezo[6]

[1]School of Medicine, UDLA University, Quito, Ecuador
[2]Department of Medicine, Armed Forces Hospital, Pastaza, Ecuador
[3]Ministry of Public Health, Quito, Ecuador
[4]Department of Medicine, Armed Forces Specialty Hospital, Quito, Ecuador
[5]IPS ARTMEDICA, Medellín, Colombia
[6]Intensive Care Unit Department, Ecuadorian Institute of Social Security, Ambat, Ecuador

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***Correspondence:**
Dr. Carlos A. Chango,
E-mail: carlosachangor@gmail.com

ABSTRACT

The alteration of adipose tissue plays a fundamental role in the appearance of chronic inflammation diseases; insulin resistance, lipid deposition in obese patients. In recent years it has been shown that under the stimulation of adipocytes in stressful situations, their endoplasmic reticulum generates a response that over activates the inflammatory response of adipose tissue and interferes with normal mentalism, generating the secretion of adipokines, affecting the thermogenic pathways of the tissue. adipose, which causes the manifestation of metabolic syndrome. This article summarizes the relationship between adipocyte endoplasmic reticulum and adipose tissue dysfunction in obese patients.

Keywords: Adipose tissue dysfunction, Endoplasmic reticulum stress, Obesity, Unfolded protein response

INTRODUCTION

Obesity is the excessive accumulation of adipose tissue resulting from a chronic imbalance between energy intake and expenditure, in most cases accompanied by inflammatory responses that are accompanied by low-grade inflammatory responses of the innate and adaptive immune systems.[1] Obesity leads to glucose intolerance and various lipid metabolic disorders that affect metabolic homeostasis. Its association with diseases such as obesity, diabetes, atherosclerosis and dyslipidemia.[2] There is an alarming increase in the number of obesity cases with around 108 million children and 604 million adults currently suffering from obesity worldwide.[3] The high cost that it generates for the health systems of each country increases in a joint manner that with the number of cases, the annual cost in prevention and treatment programs for obesity borders on 2 billion US dollars, which makes it one of the diseases with the highest costs to prevent and treat.[4] Despite the prevention and control measures to combat obesity, among which lifestyle changes, medications and surgery stand out, the development of metabolic diseases has not been effectively stopped.[5]

Recent studies indicate that the increase in endoplasmic reticulum stress (ERE) caused a significant increase in the metabolism of adipose tissue in obese people, which makes it necessary to increase research on the effects of obesity At the level of the endoplasmic reticulum (ER) protein folding, calcium homeostasis and lipid synthesis

occur. Its connection with the cell membrane is direct on the outside and inside it is attached to cell structures that form a transport of substances. The ER is essential for proper cell functioning, this is because it is responsible for the production and transport of essential cellular components.[6] Adipocytes are the main ones that form adipose tissue and actively participate in the regulation of local and systemic inflammation, insulin sensitivity and metabolism through the secretion of lipids, adipokines and cytokines, which makes it an integral part of the body's metabolism.[7]

At the adipocyte level, the ER participates in the formation of lipids and the maintenance of lipid homeostasis. The presence of ERE is taken as a cause of obesity, generating an inflammatory cascade where they cannot respond adequately and can produce and lead to chronic inflammation, insulin resistance and ectopic fat deposition in obese patients.[8] From the above, it can be observed that reducing ERE on lipid metabolism in obese patients is a great strategy to improve the metabolic syndrome (Figure 1).

Endoplasmic reticulum stress in obesity leads to the expression and secretion of adipocyte inflammatory cytokine TNF-α, MCP-1and IL-6 by affecting NF-κB, ADPN, STAMP2, LPIN1and TRIP-Br2. LPIN1 upregulates the expression of lipolytic enzymes including p-HSL and ATGL, increases fat lipolysis and increases circulating FFA. Increased TRIP-Br2 can significantly reduce the expression of Ucp1, PPARγ and other genes involved in thermogenesis, oxidative metabolism and mitochondrial biogenesis, thereby reducing the thermogenesis of adipocytes.

REVIEW

It is a descriptive-exploratory study type of bibliographic review. The literature search period is from 2014 to 2024 in electronic databases such as PUBMED, ELSEVIER and Web of Science. The keywords used in the MesH search were Endoplasmic reticulum stress, unfolded protein response, obesity, adipose tissue dysfunction. Search terms, level of evidence, summaries and keywords, exclusion criteria: not related to the topic, outside the year limit, not available. They will be classified by year, type of study and level of evidence. For eligibility, a critical reading is carried out, level of evidence, documents available for analysis and according to the topic. A total of 30 sources were obtained for analysis and synthesis.

STRESS CAUSED BY ADIPOCYTES TO THE ENDOPLASMIC RETICULUM

The endoplasmic reticulum (ER) is involved in transmembrane protein metabolism, calcium storage and lipid synthesis. In collaboration with the ribosome, the Golgi apparatus and other organelles, the ER performs multiple functions. However, when there is an exaggerated inflammatory response, calcium reserves are reduced and the imbalance of reduction and oxidation reactions (REDOX) causes homeostatic imbalance in the ER.[9]

Damage can occur in different tissues, this is secondary to the release of proinflammatory cytokines and excessive metabolic waste. Free fatty acids are normally stored in adipocytes to be used as energy, once they are used glycerol and free fatty acids are released again. Because there is little production of glycerol kinase, glycerol cannot be used and is released into the bloodstream. This causes an increase in fatty metabolites in the bloodstream, which contributes to lipotoxicity.[10]

As the misfolded proteins accumulate (folding and unfolding alterations), they are replaced by the UPR regulatory proteins described above. In the case of PERK, it causes phosphorylation of eIF2α, which causes a reduction of these proteins and the translation of factor mRNA. of transcription activator 4 (ATF4). Then an interaction occurs with C/EBP homologous protein (CHOP). This interaction continues with a phosphorylation cascade that ends in apoptosis of the affected cells.[11]

Adipocyte cells may present hypertrophy and hyperplasia. This occurs during inflammation, characteristic of obesity. Adipose tissue undergoes phenotypic and biological changes , this secondary to stress on the ER.[12]

There are multiple causes of ER stress. All of these affect the unfolded protein (UPR). Its regulation depends on inositol-requiring enzyme 1 (IRE1), double-stranded RNA-activated protein kinase R (PKR)-like ER kinase (PERK) and activating transcription factor 6 (ATF6).[9-11] The malfunction of this protein is related to alterations in the functionality and structure of the ER, such as oxidative stress, mitochondrial dysfunction, alterations in the metabolic pathway, alterations in protein folding and autophagy.[11]

Pancreatic β- cells. PERK induces stress in these cells, causing increased blood glucose levels and increases eIF α phosphorylation, which causes glucose intolerance. This leads to increased insulin production in response to hyperglycemia, which attenuates ER stress to limit and even abolish β-cell apoptosis.[13]

ER stress through the alterations it presents in the β cells of the pancreas can be considered as a trigger and aggravating factor of diabetes. The development of this disease is due to metabolic alterations of lipids and glucose, alteration of REDOX reactions, inflammations characteristic of this and alterations in insulin production and increase in basal glucose.[14]

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM AND ITS ALTERATION IN OBESITY

Obesity significantly alters the renin-angiotensin-aldosterone system (RAAS), contributing to hypertension

and various metabolic and cardiovascular complications. In obese individuals, an exacerbated activation of the RAAS is observed both systemically and in adipose tissue, leading to several pathological consequences.

First, obesity induces an increase in the production of RAAS components by adipocytes, contributing to the systemic activation of the RAAS. This increase in RAAS activity promotes the retention of sodium and water, which raises blood volume and blood pressure. Additionally, RAAS activation in adipose tissue is associated with a pro-inflammatory environment, increased lipogenesis and the generation of reactive oxygen species, worsening adipocyte dysfunction and insulin resistance.[15]

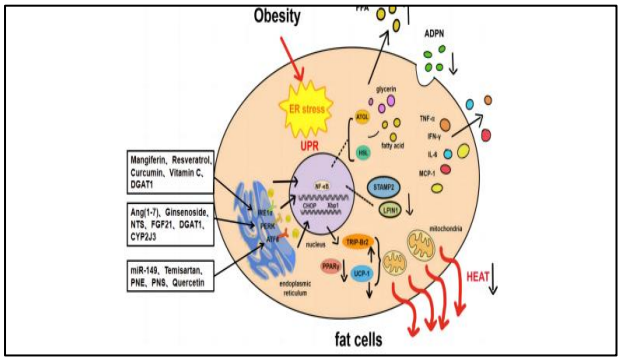

Figure 1: Main mechanisms of endoplasmic reticulum stress leading to abnormalities in adipocyte metabolism in obesity and potential drugs for intervention.[34]

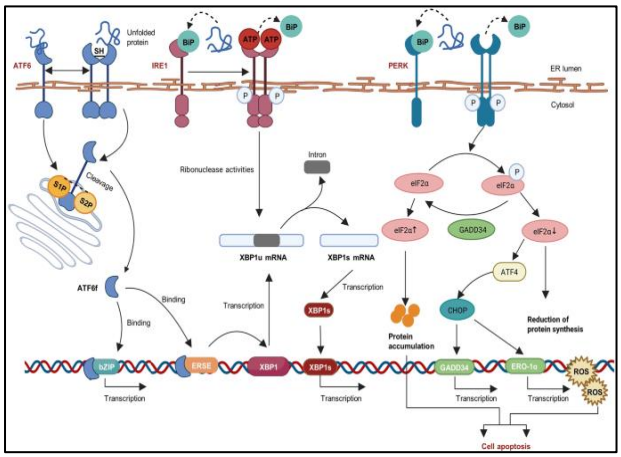

Figure 2: Unfolded protein signalling pathways (UPR).[34]

Aldosterone, a key component of the RAAS, also plays a crucial role in obesity-related hypertension. Obese individuals often exhibit hyperaldosteronism, which increases blood pressure salt sensitivity and contributes to the development of hypertension and organ damage. Aldosterone acts not only through its classic effects of retaining sodium and water but can also activate mineralocorticoid receptors in adipose tissue, promoting inflammation and fibrosis.

Furthermore, the physical compression of the kidneys by visceral and perirenal fat in obesity contributes to renal dysfunction, increasing tubular sodium reabsorption and activating the RAAS. This renal compression, together with the activation of the sympathetic nervous system, exacerbates the activation of the RAAS, creating a vicious cycle that perpetuates hypertension and renal damage.[16]

Therefore, it can be concluded that obesity induces a multifaceted activation of the RAAS, both systemically and in adipose tissue, contributing to hypertension, inflammation, renal dysfunction and insulin resistance. Understanding these mechanisms is crucial for developing effective therapeutic strategies to manage hypertension and metabolic complications in obese patients.[16]

EFFECT OF THE ENDOPLASMIC RETICULUM IN OBESE PEOPLE

For obesity there is an interaction between genetic and environmental determinants that lead to altered cellular metabolism and homeostasis, including mitochondrial dysfunction, deregulated mitophagy, macroautophagy/autophagy and ER homeostasis. The Endoplasmic Reticulum interacts with other organelles and plays an important role in protein and lipid metabolism, steroid biosynthesis, protein folding and calcium homeostasis. Impairment of these processes results in disturbed homeostasis, known as ER stress.17 Once ER stress is activated, a process called unfolded protein response (UPR) is triggered to restore ER homeostasis (adaptive UPR) or cause cell death in the case of prolonged ER stress (maladaptive/uncontrolled UPR).[17]

At the molecular level, the UPR involves three ER transmembrane proteins, eukaryotic translation initiation factor 2 alpha kinase 3 (EIF2AK3, also known as PERK), activating transcription factor 6 (ATF6) or endoplasmic reticulum-to-nucleus signalling 1 (ERN1, also known as IRE1). Their orchestrated action governs the complex network and cross-talk with intracellular events such as autophagy, inflammation and apoptosis.[20] Under normal conditions, heat shock protein A (Hsp70) family member 5 (HSPA5, also known as GRP78 or Bip), an ER-resident chaperone, binds to all three UPR components to keep them inactivated. Upon ER stress, HSPA5 dissociates from UPR components to bind to unfolded/misfolded proteins and trigger UPR activation, revealing a cardinal role for HSPA5 in regulating the UPR. Upon dissociation of HSPA5, monomeric EIF2AK3 oligomerizes and initiates a network of signaling cascades, resulting in either restoration of ER homeostasis or cell death in the face of excessive ER stress.[17] Evidence has revealed that ER stress contributes to the onset and progression of obesity through multiple mechanisms.

Function of M1/M2 macrophages

One of the main theories supporting the onset and progression of obesity is the imbalance between the

polarization of M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages. ER stress is thought to mediate an imbalance in M1/M2 macrophages.[18]

Dysregulated autophagy

A growing body of research supports that obesity may be the cause of ER stress in mammalian cells. Inhibition of ER stress effectively reversed this abnormality in diet-induced obesity. Furthermore, glutathione S-transferase kappa 1 (GSTK1, also known as DsbA-L) (an oxidoreductase-like protein critical for detoxification of cellular toxins) boosted adiponectin stability and multimerization in 3T3-L adipocytes, serving as a potential therapeutic target to offset adiponectin degradation and obesity under ER stress.[17]

Overnutrition and IKBKB-NFKB1 Signalling

Inhibitor of nuclear factor kappa B kinase subunit beta (IKBKB) denotes a subunit of the IKK complex, which regulates nuclear factor kappa B subunit 1 (NFKB1). Overnutrition is accompanied by chronic inflammation in adipose and other tissues through activation of the IKBKB-NFKB1 axis.[17] Activated NFKB1 enters the nucleus and activates inflammatory genes and immune responses. Overnutrition was shown to induce hypothalamic ER stress to activate the IKBKB-NFKB1 signaling axis, resulting in disrupted insulin and leptin signaling, inflammation and ultimately obesity in mammalian models.[18]

Uroguanylin suppression

Uroguanylin is a peptide secreted by the duodenum and functions in gut-brain regulation of food intake, metabolism and energy homeostasis.[19] In a study using mouse models of diet-induced obesity (DIO), intestinal levels of uroguanylin were reduced to dampen its release into the circulation and delivery to the brain. As a result, hypothalamic regulation of food intake was altered to promote obesogenesis. ER stress was also revealed to be the underlying mechanism of uroguanylin suppression. In this study, inhibition of ER stress using tauroursodeoxycholic acid (TUDCA) facilitated the release of uroguanylin and prevented the onset of obesity.[20] The result of this study suggests that ER stress disrupts the release of uroguanylin from the intestines, leading to disruption of hypothalamic regulation of food intake after food intake, resulting in obesity.[19]

DISCUSSION

Main mechanisms of endoplasmic reticulum stress leading to abnormalities in adipocyte metabolism in obesity and possible intervention drugs

Adipocytes in obesity have an increased demand for protein production due to the increase in adipose tissue and the considerable need for lipid synthesis. This overload leads to a significant accumulation of misfolded proteins, which activates the unfolded protein response (UPR).[22] The Unfolded Protein Response (UPR) is known as an adaptive response that seeks to restore protein homeostasis or, if stress is excessive, induces apoptosis.[23]

The key sensors of the UPR are PERK (Protein kinase RNA-like endoplasmic reticulum kinase), inhibits protein translation to reduce ER load.[23] IRE1 (Inositol-requiring enzyme 1), facilitates the degradation of misfolded messenger RNA and activates proinflammatory factors.[23] ATF6 (Activating transcription factor 6), increases the production of chaperones that help protein folding.[23]

Chronic ER stress in adipocytes promotes cell apoptosis, increased inflammatory cytokines and insulin resistance.[24] Within obesity, an exaggerated accumulation of triglycerides and fatty acids is observed in adipocytes, this overloads the ER and alters lipid metabolism. This accumulation of lipids, apart from generating reactive oxygen species (ROS), also compromises the proper folding of proteins.[25,26]

Alteration in lipid synthesis

Endoplasmic reticulum stress modifies lipid homeostasis, impairing the biogenesis of lipid proteins and causing metabolic dysfunction. Thus, lipid oxidation creates an inflammatory state that further impairs adipocyte function.[24] Chronic activation of the UPR is manifested through the IRE1 pathway, leading to the activation of NF-κB and JNK, at this level it promotes the secretion of cytokines such as TNF-α, IL-6 and MCP-1. These cytokines increase inflammation in adipose tissue, which contributes to insulin resistance and other metabolic disorders.[27]

Tauroursodeoxycholic (TUDCA) it is a bile acid that improves the function of the Endoplasmic Reticulum, facilitating the proper folding of proteins and reducing ER stress. It has shown positive and promising effects to improve insulin resistance and glycemic homeostasis in obesity prototypes. [28,29] 4-Phenylbutyric acid (PBA) it is a component that acts as a chemical chaperone, helping to reduce the accumulation of misfolded proteins and improving ER stress. It improves the function of adipocytes and reduces the inflammation process.[30]

UPR modulators

IRE1α inhibitors are drugs that inhibit IRE1α activity could prevent the activation of proinflammatory pathways without compromising the adaptive function of the ER. Examples include compounds such as MKC-3946, which inhibits the IRE1-XBP1 pathway.[31] PERK inhibitors: One of the specific PERK inhibitors, such as GSK2656157, is being studied to limit the negative impact of the UPR on metabolic function.[32] Drugs targeting SREBP (Sterol regulatory element-binding proteins) it has been investigated that they modulate lipid synthesis in the ER

and help to improve lipid overload within adipocytes, improving ER stress and metabolic function.[33]

CONCLUSION

This article summarizes the relationship between adipocyte endoplasmic reticulum and adipose tissue dysfunction in obese patients

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