

ENDOPLASMIC RETICULUM STRESS MARKERS EXPRESSION LEVELS IN LEPTIN RESISTANCE DEVELOPMENT

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Abstract

This review explores the link between endoplasmic reticulum (ER) stress and leptin resistance in obesity, with a focus on women. ER dysfunction activates stress markers such as XBP1, CHOP, and GRP78, disrupting leptin signaling and promoting metabolic imbalance. Chronic overnutrition induces sustained ER stress, impairing hypothalamic and peripheral leptin pathways. Elevated expression of these markers correlates with obesity severity and metabolic dysfunction, particularly in females due to hormonal and fat distribution differences. Understanding these molecular mechanisms may guide the development of targeted therapies for obesity-related disorders.

Keywords: Leptin, obesity, stress, xbp1, chop, grp78, resistance, adipose, gene, expression, women, cytokines, hormone, er, metabolism.

Introduction

The global obesity epidemic has emerged as one of the most pressing public health challenges of the 21st century, affecting millions of individuals worldwide and contributing substantially to metabolic disease burden. Central to understanding obesity pathophysiology is leptin, a 16-kDa adipocyte-derived hormone discovered in 1994 that revolutionized our comprehension of energy homeostasis. Leptin functions as a crucial adiposity signal, communicating the status of energy stores to the central nervous system, particularly the hypothalamus, where it regulates appetite, energy expenditure, and neuroendocrine function. Under physiological conditions, increasing adipose tissue mass leads to proportional leptin secretion, which then acts on hypothalamic receptors to suppress appetite and increase metabolic rate, creating a negative feedback loop that maintains energy balance.

However, the paradox of obesity lies in the phenomenon of leptin resistance, wherein elevated circulating leptin concentrations fail to elicit appropriate physiological responses despite intact receptor expression. This resistance mechanism shares conceptual similarities with insulin resistance in type 2 diabetes, representing a fundamental breakdown in hormonal signaling that perpetuates metabolic dysfunction. Obese individuals typically exhibit hyperleptinemia, yet remain insensitive to the hormone's anorexigenic and thermogenic effects, creating a vicious cycle of continued weight gain and metabolic deterioration. The molecular mechanisms underlying leptin resistance remain incompletely understood, though multiple contributing factors have been identified, including impaired blood-brain barrier leptin transport, receptor downregulation,



enhanced suppressor of cytokine signaling (SOCS) protein expression, and inflammatory pathway activation.

Women demonstrate particular vulnerability to obesity-related metabolic complications, influenced by hormonal fluctuations across reproductive life stages, distinct adipose tissue distribution patterns favoring subcutaneous rather than visceral deposition in premenopausal years, and sex-specific differences in energy metabolism. The postmenopausal transition frequently precipitates visceral fat accumulation and metabolic deterioration, coinciding with declining estrogen levels that previously conferred relative metabolic protection. Understanding sex-specific mechanisms in leptin resistance development holds significant clinical relevance for designing personalized therapeutic approaches. Recent investigations have illuminated the critical role of endoplasmic reticulum stress in metabolic disease pathogenesis, including leptin resistance development. The endoplasmic reticulum constitutes a vast intracellular membranous network responsible for protein synthesis, folding, modification, and quality control, alongside calcium storage and lipid biosynthesis. Cellular stressors including nutrient excess, lipid accumulation, inflammatory cytokines, and oxidative stress can overwhelm ER protein-folding capacity, leading to accumulation of misfolded or unfolded proteins within the ER lumen. This condition, termed ER stress, triggers the unfolded protein response, an adaptive signaling cascade aimed at restoring ER homeostasis through multiple mechanisms: attenuating protein translation to reduce ER client load, enhancing ER-associated degradation to eliminate misfolded proteins, and upregulating molecular chaperones to improve folding capacity.

The UPR operates through three principal transmembrane sensors: inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase (PERK), and activating transcription factor 6 (ATF6). Under non-stressed conditions, these sensors remain inactive through association with the ER chaperone GRP78. Upon ER stress, GRP78 preferentially binds accumulated unfolded proteins, liberating the three sensors to initiate downstream signaling cascades. While acute ER stress activation promotes adaptive responses facilitating cellular survival, chronic ER stress engagement, as occurs in obesity, triggers maladaptive responses including inflammation, insulin resistance, and apoptosis, contributing directly to leptin resistance development. This review synthesizes current understanding regarding specific ER stress markers-XBP1, CHOP, and GRP78-and their roles in leptin resistance pathophysiology, with particular emphasis on expression patterns observed in obese women. By elucidating these molecular mechanisms, we aim to identify potential therapeutic targets for addressing this critical metabolic disorder.

Results and discussion

The molecular architecture of ER stress response involves coordinated activation of specific markers that serve both adaptive and, when chronically engaged, maladaptive functions in metabolic regulation. Understanding how these markers interact with leptin signaling pathways provides essential insights into resistance mechanism development.

XBP1 is a key transcription factor in the IRE1 branch of the unfolded protein response (UPR). Under ER stress, IRE1 splices XBP1 mRNA to form active XBP1s, which regulates genes for protein folding, ER expansion, and inflammation. In obesity, hypothalamic XBP1s levels rise, promoting inflammation (via TNF- α , IL-6) and impairing leptin signaling through JNK and IKK activation.



Chronic XBP1 activity in adipose tissue increases systemic inflammation and alters adipokine secretion. Studies in obese women show higher XBP1s expression in visceral fat, correlating with inflammation and insulin resistance.

CHOP (GADD153) is a pro-apoptotic transcription factor induced by prolonged ER stress through PERK-ATF4 and ATF6 pathways. In diet-induced obesity, elevated CHOP in hypothalamic POMC neurons triggers apoptosis and reduces leptin responsiveness. CHOP also suppresses JAK-STAT signaling genes, worsening leptin resistance. In adipose tissue, CHOP promotes lipolysis and fatty acid release, leading to systemic lipotoxicity. Obese women show increased CHOP expression correlating with BMI and reduced leptin sensitivity.

GRP78 (BiP/HSPA5) is the main ER chaperone regulating protein folding and UPR activation. Chronic overnutrition elevates GRP78 expression, indicating persistent ER stress. In obesity, hypothalamic GRP78 upregulation reflects long-term stress and contributes to leptin resistance. While overexpression may transiently protect neurons, prolonged activation becomes maladaptive. GRP78 also appears on cell surfaces, participating in inflammatory signaling that disrupts leptin receptor function. Elevated GRP78 in visceral adipose tissue and serum of obese women correlates with inflammation, high leptin levels, and metabolic dysfunction, suggesting its potential as a biomarker of leptin resistance.

Women show distinct adipose tissue distribution and hormonal patterns that influence obesity-related metabolic risks. Studies consistently demonstrate that ER stress markers—XBP1s, CHOP, and GRP78—are significantly upregulated in obese women, correlating positively with BMI, waist circumference, and visceral fat volume. Visceral adipose tissue shows stronger marker expression than subcutaneous fat, linking it to greater metabolic risk, especially in postmenopausal women where estrogen decline enhances ER stress activation. Weight loss interventions, such as bariatric surgery or lifestyle modification, markedly reduce these ER stress markers alongside improved leptin sensitivity, supporting a causal link between ER stress and leptin resistance. Mechanistically, ER stress in adipocytes promotes secretion of pro-inflammatory cytokines (TNF- α , IL-6, IL-1 β) and free fatty acids, inducing systemic inflammation and hypothalamic lipotoxicity that impair leptin signaling. Animal studies confirm hypothalamic upregulation of XBP1s, CHOP, and GRP78 during diet-induced obesity, preceding leptin resistance. Estrogen appears protective by enhancing ER resilience, explaining slower leptin resistance progression in females before menopause. Genetic polymorphisms in XBP1 and GRP78 genes may further modulate susceptibility to metabolic dysfunction. Chronic overnutrition causes a transition from adaptive to maladaptive ER stress, marked by sustained CHOP activation and persistent inflammation, coinciding with leptin resistance onset. Therapeutically, chemical chaperones (4-PBA, TUDCA) reduce ER stress and restore leptin sensitivity in experimental models, while dietary control and exercise naturally modulate ER stress pathways. Diets rich in unsaturated fats and regular physical activity enhance ER homeostasis and may offer practical strategies to mitigate leptin resistance in women.

In conclusion, chronic endoplasmic reticulum stress involving XBP1, CHOP, and GRP78 disrupts leptin signaling, leading to inflammation and neuronal dysfunction. In women, elevated levels of these markers correlate with obesity severity and hormonal changes. Reducing ER stress may help prevent metabolic complications and improve leptin sensitivity.



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