



THE ROLE OF ENDOPLASMIC RETICULUM STRESS IN THE RELATIONSHIP BETWEEN METABOLIC SYNDROME AND LEPTIN RESISTANCE IN WOMEN

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Annotation

Metabolic syndrome in women is frequently accompanied by leptin resistance, yet the underlying cellular mechanisms remain incompletely understood. This study examines how endoplasmic reticulum (ER) stress contributes to impaired leptin signaling in female patients with metabolic syndrome. We investigate the activation of ER stress markers including GRP78, XBP1, and CHOP, and their impact on leptin receptor function and downstream signaling pathways, proposing ER stress modulation as a potential therapeutic target.

Keywords: endoplasmic reticulum stress, leptin resistance, metabolic syndrome, obesity, unfolded protein response (UPR), inflammation, adipose tissue, hypothalamus, women, estrogen, insulin resistance, metabolic dysfunction, Metabolic syndrome affects women differently than men, with distinct patterns of adipose tissue distribution and hormonal influences shaping disease progression. Leptin, a hormone secreted primarily by adipocytes, normally regulates energy balance and body weight through hypothalamic signaling. However, in obesity, paradoxically elevated leptin levels fail to suppress appetite or increase energy expenditure-a phenomenon termed leptin resistance. Women with metabolic syndrome demonstrate pronounced leptin resistance alongside insulin resistance, creating a vicious cycle that perpetuates weight gain and metabolic dysfunction. The mechanisms linking chronic nutrient excess to leptin resistance remain unclear, though recent evidence points toward cellular stress responses in adipose tissue and hypothalamic neurons as critical mediators. Understanding these pathways in female-specific contexts is essential given sex differences in adipokine profiles and metabolic disease risk.



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Endoplasmic reticulum stress occurs when the protein-folding capacity of the ER becomes overwhelmed, triggering the unfolded protein response (UPR). In obesity, excessive lipid accumulation and chronic inflammation activate the UPR in adipocytes and hypothalamic neurons. Three key ER stress markers reflect this activation: GRP78 (glucose-regulated protein 78), the master regulator that initiates the UPR; XBP1 (X-box binding protein 1), which promotes adaptive responses through transcriptional regulation; and CHOP (C/EBP homologous protein), which drives apoptotic pathways during prolonged stress. Evidence indicates that ER stress directly impairs leptin signaling. In hypothalamic neurons, elevated GRP78 expression correlates with reduced JAK2-STAT3 phosphorylation following leptin stimulation, effectively blunting the hormone's anorexigenic effects. XBP1 splicing, another ER stress indicator, increases inflammatory cytokine production in adipose tissue, further disrupting leptin receptor sensitivity. Meanwhile, CHOP upregulation promotes adipocyte dysfunction and death, reducing leptin secretion quality and amplifying systemic metabolic disturbances. The relationship between ER stress and insulin resistance compounds these effects. ER stress activates JNK and IRS-1 serine phosphorylation, inhibiting insulin receptor signaling—a pathway that overlaps significantly with leptin resistance mechanisms. In women, hormonal fluctuations and preferential subcutaneous fat deposition may modulate ER stress responses differently than in men, though this area requires further investigation. Studies demonstrate that hypothalamic ER stress in female rodents induces more severe leptin resistance compared to males, possibly due to estrogen's complex interactions with UPR pathways.

Endoplasmic reticulum stress represents a critical node connecting obesity, leptin resistance, and metabolic syndrome in women. Interventions targeting ER stress—whether through chemical chaperones, lifestyle modifications, or novel therapeutics—may restore leptin and insulin sensitivity simultaneously. Future research should investigate sex-specific ER stress responses and develop targeted approaches that account for hormonal influences on UPR activation. Reducing ER stress burden offers promise for breaking the cycle of leptin resistance and metabolic dysfunction in affected women.



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