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The Role of Leptin and Estrogens as Key Factors in Obesity

Obesity is caused by a combination of genetic and environmental factors (epigenetic). To understand the etiopathogenicity of obesity and certain hormone-dependent cancers, recent studies have indicated the importance of cross talk between estrogens and the signal pathway of leptin. As we shall see, hyperleptinemia reflects the activity of aromatase, ER- α , thus increasing levels of estrogens circulating in blood or more importantly, increasing levels of active intracellular estrogens “in situ”. Obese individuals have higher levels of circulating estrogens. Reciprocally, the estrogenic predominance and biological activation of ER- α also reflect the major fabrication of leptin in adipocytes with the consequential increase in weight. When we learn that the estrogen receptor alpha (ER- α) and the leptin receptor (Ob-R) are expressed jointly we are presented with questions such as: what influences more in obesity, sugary drinks? Foods rich in estrogens? Or perhaps BPA and phthalates from plastics that act as endocrine disruptors in the signal receptor? Leptin gene expression could be modulated by activation of estrogen receptors.

Regulation of leptin synthesis: The excess of corporal fat in obesity is related with the excess of estrogens, insulin, IGF, leptin, systemic inflammation and/or local inflammation of adipose tissue and alterations in immunity. The level of ob mRNA in white adipose tissue and the circulating leptin concentration are increased markedly in obesity, as shown in both human studies and in studies of several types of obese animal. Indeed, in human subjects there is a high correlation between body mass index (BMI) and circulating leptin. Thus, the greater the amount of adipose tissue, the higher the level of the hormone. In addition, adipocyte size appears to be another major determinant of leptin mRNA expression. In humans leptin expression appears to be greater in subcutaneous than in omental adipose tissue.

Low levels of leptin are found in lean humans and animals: In contrast, individuals whom are overweight or obese, we find high levels of plasmatic leptin since it is positively related with an increase in corporal weight, the body mass index (BMI) and percent of corporal fat. The serial levels of leptin reflect the amount of stored fat in adipose tissues (disposable energy) and is proportional to the total corporal adipose tissue in rats as in humans. The level of activity of mRNA of leptin (ob mRNA) in adipocytes of obese individuals is two times more than those of normal weight and the leptin circulating in the plasma of those with obesity is greater than three times more in comparison with normal weighing individuals.

The differences in mRNA level between various adipose tissue sites may reflect differences in fat cell size; the larger the adipocytes, the greater the expression of the ob gene. Indeed, females express 2-3 higher leptin levels than males after normalizing for body fat mass and age; these differences were ascribed to estrogens (Ahima & Flier 2000). It is possible that estrogens may stimulate and androgens may suppress leptin production respectively. Leptin is a hormone produced and secreted specifically in adipose tissue (WAT), in pre-adipocytes and adipocytes (the larger adipocytes fabricate more leptin), and also fabricated in the placenta, ovaries, brain, epithelial cells of breasts, cells of the gastric mucosa, myocytes of skeletal muscle and medullary osseous tissue. ?Regulates physiologically the corporal weight and promotes satiety in the hippocampus and regulates the energy expenditure after ingestion of food as well as increasing thermogenesis. However, in pathophysiological conditions such as obesity, leptin, the leptin receptor (ObR) and the mediators in the signal pathway that respond to leptin can ruin one's life: obesity, Type 2 Diabetes Mellitus, cardiac diseases, apneas, infertility, autoimmunity, cancer, etc. In addition to greater

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production of leptin, individuals with obesity may also be insensitive to endogenous leptin, thus creating a leptin-resistant state (40,41). This leptin-resistant state is thought to be a result of several mechanisms such as defective leptin transport across the blood-brain barrier, attenuation of leptin signaling through the inactivation of the JAK-STAT pathway (via inhibition by suppressor of cytokine signalling-3), endoplasmic reticulum stress and inflammation. Given this dys-regulation in the leptin signaling cascade, greater amounts of leptin are continually released from the adipose tissue of individuals with obesity. In chronic hyperleptinemia we will not see an appropriate response to the decrease in ingestion of food and the increase in the energy expenditure due to the decrease in sensitivity of hypothalamic receptors of leptin in which we will then begin to have resistance to insulin and begin to gain weight. Despite the attenuation of the JAK-STAT pathway in leptin resistance, the ability of leptin to stimulate cell proliferation is sustained through activation of other cell signaling pathways such as phosphoinositide3kinase (PI3K)/AKT pathway and mitogen-activated protein kinase pathway (MAPK) pathway (43). Therefore, leptin remains a likely candidate for promoting tumorigenesis in obesity-driven, postmenopausal breast cancer, even in a leptin-resistant state.

Crosslink of leptin and ER- α : Leptin can control the expression of ER- α mRNA and aromatase via ERK and STAT3 as well as directly activate ER- α . Leptin induces hyperestrogenism and alters the estrogenic metabolism, in vitro and in vivo by:

major expression of mRNA and more activity of aromatase that conditions an increase production of local estrogens, especially in postmenopausal women.

- major expression of mRNA and activity in ER- α , independently of the presence of its endogenic ligand, estrogen (E2-ER).
- increase in sensitivity of the mammary tissue to estrogens through an increase in expression of ER- α .-increase activity of CYP 1B through the induction of the ERK and AKT pathways increasing the metabolite of estrogens 4-OHE1/E2.
- reduction in the activity of the methylation enzyme (COMT) which implicates a bad detoxification of the catechol-estrogens 2-OH E1/E2 and 4-OH E1/E2 in their methylated forms (2-MeOE1/E2 and 4MeOE1/E2). Consequently they are oxidized to semiquinone (SQ) and quinone (Q) that will react with our DNA if they are not detoxified.
- reduction in the enzyme activity of NQO1. This is the enzyme that helps us detoxify the quinines formed by incomplete methylation of estrogens to an initial hydroxylated form (2-OH and 4-OH estrogens) given another possibility at methylation (COMT) of estrogens and protecting our DNA and the formation of adducts with mutagenic potential.

The lack of NQO1 leads us to an increase production of adducts of quinines (N3-adenine, N7-adenine and N7-guanine) or oxidative stress in our DNA by redox reactions of quinines-semiquinines. In this situation, reacting with our DNA and lead to mutations and condition the proliferation of cancer in breast or prostate. We find increased levels of leptin in this proportion: healthy people < breast benign diseases patients < breast cancer patients < lymph node metastasis positive patients

Healthy women without breast cancer have lower levels of leptin: It has been observed that an overexpression in 92% of the leptin in leptin receptors in breast tumors, in contrast, it has not been detected in epithelial cells of breasts in healthy women, suggesting that leptin fabricated by adipocytes can have an autocrine and paracrine activity in cancerous cells of breast, apart from the classic endocrine activity of leptin circulating in blood that has biological activity in susceptible tissues. In multiple epidemiological studies and a meta-analysis by Niu et al in 2013 it was proved that a clear association between obesity and elevated levels of leptin in plasma has an increased risk to predispose to breast cancer in women. Studies performed in women with cancerous cells (ER)-positive of breast, leptin increased the expression of mRNA in the enzyme aromatase in the adipose tissues as well as increasing the quantity and activity of the enzyme aromatase via ERK and Stat3. Concomitantly, the elevation of leptin also increased the levels of estrogens in the blood. The major activity of aromatase in adipose tissue induced by leptin, pro-inflammatory cytokines, PgE2 and insulin are to increase the local production of estrogens and the signaling of the ER in cancerous cells of breast (MCF-7). In obesity we have an increased activity of the enzyme aromatase, the enzyme coded by CYP19A that converts androgens to estrogens. Women with obesity produce more androstenedione and the result is that these women with elevated BMI's, through increased activation of aromatase, is an increase in circulation of estrogens in the blood

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and in situ. The excess of estrogenic exposure during our lives is determined by early menarche, late menopause or by obesity and are all associated by an increase in risk in developing breast cancer in postmenopausal women.

What happens with the hyperactivation of aromatase?: We know that the presence of estradiol in the cells (intracellular) by activation of aromatase stimulates an increase in production of leptin by fat cells.

This excess of estrogens promotes:

- insulin resistance
- reduces insulin receptor function
- inhibits the gene expression of the insulin receptor for insulin in a dose dependent fashion.
- worsens the sensitivity to insulin.
- hyperinsulinemia: reactivates many factors that inhibit leptin receptors.
- resistance to leptin
- hyperleptinemia
- abnormal induction of growth and alteration of cellular apoptosis.

Leptin and estrogen connection: there exists an important reciprocal functional dependence between estrogens and leptin. Estrogens exert an important influence with adipokines fabricated by adipocytes (adiponectin, resistin, leptin). The levels of estrogens are inversely related with the levels of plasmatic adiponectin. Thus the increase of estrogens reduce adiponectin. Resistin, adipokines which favor obesity also decrease when estrogens increase. In contrast, the levels of estrogens in premenopausal women are narrowly related to levels of leptin. Increased levels of estrogens also induce hyperleptinemia.

Estrogens also modulate the function of leptin:

- increased expression of mRNA of leptin in its secretion in adipose tissue.
- estrogens increase the sensitivity of leptin controlling the expression of the leptin receptors.
- increased intratumoral levels of leptin in ER+ cancers are specifically related with the stimulation and growth of cancer through autocrine mechanisms. The surgical excision of breast cancer tumors does not extensively influence the quantity of circulating leptin in blood since the quantity of leptin production produced by tumor cells are minimal and in contrast are attributed primarily to adipose tissue since it is most responsible for most of the circulating leptin.

That there is a direct association between expression of ER α and LepR in breast cancer samples obtained from women at different stages of the disease. This association may also act as a novel marker in the clinical follow-up of the tumor. Finally, these data also set the cellular and molecular basis for a novel therapeutic approach in breast cancer aimed at targeting LepR. This interaction is testified by the evidence that the treatment of ER α -positive MCF cell line 7 with r-leptin induces an upregulation of both LepR itself and ER α . These effects were not observed when breast cancer cells did not express LepR. Also, these mechanisms are linked to each other. Inhibition of leptin receptor by siRNA leads to down-regulation of ER α gene expression (Fusco et al., 2010). We observed robust correlation between ER α positivity and high LepR expression. On the contrary, the majority of ER α -negative patients did not express significant levels of LepR. This also suggests that the LepR may be considered as a novel marker of the differentiation of breast cancer, despite its potential role in mammary cell transformation. Thus, modulation of each involving gene (leptin, leptin receptors, ER) can cause interference in the entire pathway in ER+ cells and based on these mechanisms, the synergistic inhibitory effects of curcumin and silibinin on leptin expression are, therefore, due to their effects on the same targets.

In conclusion, we demonstrated that, for example, silibinin-curcumin mixture could potently inhibit expression and secretion of leptin in T47D breast cancer cell line. Regarding to the significant roles of leptin and leptin receptor in breast carcinogenesis, its inhibition by curcumin and silibinin could be considered as a novel strategy for treatment of breast cancer in the future.