We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Leptin and Its Role in Oxidative Stress and Apoptosis: An Overview

*Volkan Gelen, Abdulsamed Kükürt, Emin Şengül
and Hacı Ahmet Deveci*

Abstract

Adipose tissue (AT) in the body plays a very important role in the regulation of energy metabolism. AT regulates energy metabolism by secreting adipokines. Some of the adipokines released are vaspin, resistin, adiponectin, visfatin and omentin, and leptin. In addition to regulating energy metabolism, leptin plays a role in the regulation of many physiological functions of the body such as regulation of blood pressure, inflammation, nutrition, appetite, insulin and glucose metabolism, lipid metabolism, coagulation, and apoptosis. Among all these physiological functions, the relationship between leptin, oxidative stress, and apoptosis has gained great importance recently due to its therapeutic effect in various types of cancer. For this reason, in this study, the release of leptin, its cellular effects and its effect on oxidative stress, and apoptosis are discussed in line with current information.

Keywords: Apoptosis, leptin, obesity, oxidative stress

1. Introduction

Obesity is defined as a chronic disease that results in an increase in adipose tissue (AT) in the body as a result of the energy intake being more than the energy spent. Today, it has become a common and important health problem in both developed and developing countries due to various reasons such as changes in eating habits and inactivity [1, 2]. Obesity directly or indirectly affects national economies. Obesity causes an increase in the rates of noncommunicable diseases, damage to various organs, shortens the life span, and negatively affects the quality of life [3–5]. In the case of obesity, which is so important, the level of leptin increases. Leptin is an adipokine secreted in fat cells [6]. After leptin is released from the fat cell, it reaches the central nervous system via the blood, binds to its receptor, and reduces food intake through this receptor [7, 8]. Leptin is produced by the obese (*ob*) gene in adipose cells by encoding it into mRNA [9, 10]. As the number of fat cells in the body increases, the plasma leptin level also increases. While leptin decreases plasma glucose and insulin levels, it increases metabolic rate and physical activity, resulting in a decrease in body fat [11]. It has been determined that leptin, which has such important effects on fat cells and hunger, is effective on cancer cells. In line with this information, this study aimed to explain leptin synthesis, its receptor, factors affecting its release, and the relationship between leptin, oxidative stress, and apoptosis.

2. Leptin

Leptin (a fat tissue hormone), the *ob* gene product, was the first adipokine discovered. Its discovery is based on work done in the 1950s. It begins with the researchers' discovery of two genes, called diabetic (*db/db*) and obese (*ob/ob*), in two separate strains of mice [12, 13]. In a study conducted in these mice, which have the same phenotypic characteristics (such as insulin resistance, morbid obesity, lethargy, and infertility), blood leptin level was found to be deficient in the *ob/ob* gene product, while the *db/db* gene product was found to have a deficient leptin receptor. In addition, in the study where *db* and *ob* genes were examined in detail, *db/db* and *ob/ob* mice were both three times heavier than controls, and both groups of animals had five times more fat than the control [14]. About 40 years after the first studies, the *ob* or *Lep* gene encoding leptin was discovered and given this name because of its weak meaning [15]. About a year later, the isolation of the leptin receptor gene was reported [16].

The mouse leptin gene size is 4.5 kilobases long containing 167 amino acids [15]. Regulation of the leptin gene initiator that controls leptin production, is mediated by glucocorticoid response elements, CCAAT/enhancers, cyclic adenosine monophosphate (cAMP), and specificity protein 1 (SP1) binding sites [17]. Studies have shown that human leptin is 84% similar to mouse leptin and 83% to rat leptin [18]. Besides, a positive correlation was found between plasma leptin concentrations and AT leptin mRNA levels. Therefore, as leptin mRNA increases, plasma leptin concentrations also increase [19].

Human leptin is produced from a gene on chromosome 7. The structure of human leptin, a 16 kilodalton protein, is in the form of a 4 α helical bundle coil, like class-I helical cytokines [20]. The most highly conserved amino acid extension is the GLDFIP sequence [21, 22]. Leptin, synthesized by adipocytes, is a hormone that notifies the brain of energy reserves and affects metabolism, reproduction, growth, and development processes [16, 22]. Circulating leptin levels act at the hypothalamic central level to increase energy expenditure and reduce food intake when the body is well nourished [23]. It induces the storage of triglycerides in AT and has an effect on appetite [7]. When plasma leptin levels increase, it sends a signal of satiety to the brain in the short term, while it sends information about the energy status in the long term [24]. It also influences hypothalamic neuropeptide signaling [25]. The main physiological role of leptin during periods of hunger is to regulate the neuroendocrine system. With regard to obesity, leptin levels rise with increasing adiposity [26]. Circulating leptin levels are high in obese, pointing to the importance of leptin resistance in the obese [24]. Leptin-deficient mice have been found to show neuroendocrine abnormalities similar to starving mice. Leptin supplementation causes neuroendocrine normalization and reduced food intake in leptin-deficient obese rodents and humans, thereby reversing obesity [10]. Mutations of the *ob* gene result in leptin resistance and extreme obesity in mice [15]. *Ob/ob* mice have neuroendocrine abnormalities and they are generally classified as hyperphagic, hypothermic, morbidly obese [27].

It has been reported that leptin plays a proinflammatory role by increasing the inflammatory immune response, and this is associated with the pathogenesis of many complications of obesity [28]. It is noted that leptin can affect both adaptive and innate immunity by inducing proinflammatory response and thus playing a key role in regulating the pathogenesis of various autoimmune/inflammatory diseases [29]. It has been shown that as the degree of obesity increases in adults, the levels of plasminogen activator inhibitor-1 (PAI-1) and leptin, which is a proinflammatory marker, increase. It has been reported that it is responsible for the proinflammatory process, which is associated with an increased level of obesity [30]. Leptin regulates

the functions of immune cells, such as natural killer cells, dendritic cells, neutrophils, eosinophils, macrophages, and basophils [23].

3. Leptin synthesis

Effector systems that control energy intake and energy expenditure, hypothalamic control centers where leptin signals from different sources are received, and the size of AT mass are the regulatory steps of leptin synthesis [31]. The major sites of leptin mRNA expression are in the stomach, liver, and AT [32]. Leptin mRNA is also expressed at minor levels in the fetal tissue, placenta, heart, brain, and pituitary gland [18]. Leptin synthesized is generally related to the degree of adiposity. Larger adipocytes express more leptin genes than smaller adipocytes [33]. Mechanical stretching of the fat cell, determined by the amount of stored triglycerides, can generate signals to increase leptin synthesis [24]. In addition, in humans, uridine diphosphate N-acetylglucosamine (UDPGlcNAc) and hexosamine act as potential links between cell size and leptin content. Body mass index is positively correlated with the amount of UDPGlcNAc in subcutaneous AT [34].

The composition of the food, not the amount, affects leptin production [35]. The composition of a meal affects leptin levels; for example, low-fat and high-carb food causes increased leptin levels [36]. Compared to high-carbohydrate meals, high-fat meals lower circulating plasma leptin levels 24 hours after a meal [37]. It has been reported that meals rich in ω -6 polyunsaturated fatty acids (PUFA) increase leptin production [35]. It has been reported that the protein composition of a meal does not affect leptin production [38].

Gender differences have an effect on leptin production. Although there is no difference in leptin levels between girls and boys in the prepubertal period, leptin levels increase in girls and decrease in boys with puberty development [39, 40]. This is explained by the fact that with puberty, the amount of body fat in girls increases more than in boys, and testosterone suppresses leptin levels in boys [41]. In addition, the fact that the subcutaneous AT mass is significantly larger than the omental fat mass of women is also among the factors [39]. Reproductive hormones greatly affect leptin production. Androgenic hormones inhibit leptin synthesis, while estrogens stimulate leptin synthesis [42]. In one study, it was thought that increased estrogen concentrations caused an increase in leptin concentration, which may have been caused by leptin stimulating gonadotrophin releasing hormone (GnRH) synthesis and thus increasing estrogen synthesis [43]. In addition, chronic insomnia and an increase in melatonin concentrations have been reported to decrease plasma leptin concentrations [44].

4. Leptin release factors

The immune system has a role in regulating energy expenditure and AT lipolysis [45]. White adipose tissue (WAT) is the primary energy store; brown adipose tissue (BAT) is associated with heat production. Sympathetic activity in WAT is increased in conditions associated with decreased leptin synthesis/secretion, such as cold exposure and starvation. By the way, catecholamine and β -adrenoceptor agonists inhibit leptin production; this suppressive effect is mediated by β 3-adrenoceptor agonists, which actively reduce leptin levels [46]. Leptin also causes sympathetic nervous system activation, resulting in regulatory feedback inhibition [47]. Intracerebroventricular injections of leptin have been noted to increase metabolic rates through increased norepinephrine release from sympathetic nerve terminals innervating BAT [48].

After a meal, plasma insulin and amino acid levels initiate the mammalian target of rapamycin (mTOR) pathway, which stimulates leptin biosynthesis via mechanisms involving the 5'/3' untranslated region (UTR) [49]. Cyclic AMP activates cyclic AMP-activated exchange proteins (EPACs). Deletion of *EPAC1* genes causes an increase in leptin sensitivity in the hypothalamus. *EPAC1* is also involved in leptin secretion and expression in WAT [50].

Leptin antagonizes orexigenic pathways and stimulates anorexigenic pathways. Leptin exerts its general effects on the nervous system through these pathways [7]. Orexigenic neuropeptides that are down-regulated by leptin are orexins, agouti-related peptides, neuropeptide Y, and melanin-concentrating hormone. By the way, the anorexigenic neuropeptides upregulated by leptin are alpha-melanocyte-stimulating hormone, which acts on corticotropin-releasing hormone, cocaine and amphetamine-regulated transcript, and melanocortin-4 receptor (**Figure 1**) [31].

Glucocorticoids are long-term regulators of leptin expression [52, 53]. They increase leptin mRNA levels by acting on adipocytes; *in vitro* incubation of a synthetic glucocorticoid in rats, adipocytes have been found to increase leptin secretion [54]. Oral glucocorticoids doubled serum leptin levels and leptin mRNA 24–48 hours after absorption. Furthermore, cell cultures incubated with a glucocorticoid and insulin combination synergistically increased leptin mRNA levels [55].

Lactates and hexoses also increase leptin secretion [56]. Because leptin secretion requires ATP, suppressing glucose uptake suppresses leptin secretion. When the energy supply is low, food is needed to increase it. Glucose, the cellular sensor of energy stock, stimulates leptin gene expression and secretion in both muscle and AT via hexosamine biosynthetic [57]. Insulin lowers blood sugar when glucose levels rise above normal and also increases leptin promoter activity [58]. No increase in leptin mRNA levels was observed after adipocytes were incubated with insulin for 1–2 hours, but an increase in leptin release was observed [54].

Regulation of tumor necrosis factor-alpha(TNFα) and leptin may be inter-dependent and similar as they have comparable functions such as suppressing

Figure 1. The leptin/Melanocortin pathway. ARC; the arcuate nucleus of the hypothalamus, POMC; proopiomelanocortin, Ob-R; leptin receptor, PVN; paraventricular nucleus, MSH; melanocyte-stimulating hormone (α-MSH,β-MSH,γ-MSH), MC4R; melanocortin-4 receptor, SIM1; single-minded 1 [51].

lipid synthesis, reducing food intake, and stimulating lipolysis [59]. Leptin limits AT mass. TNF α has the role of stimulating leptin secretion from mature human adipocytes. TNF α therapy has been shown to cause increased leptin levels in humans [60].

5. Leptin receptor and leptin resistance

Leptin receptors are in the family of cytokine receptors. There are six isoforms encoded by the *LepR* gene. The *OB-Rb* receptor is the dominant longest form. Its mutations cause obesity because it cannot bind to the receptor [16]. Obese people have high leptin levels. Circulating leptin levels are correlated with body mass index [61]. On the other hand, in diet-related exogenous obesity, studies in fat mice and humans without leptin deficiency, it has been shown that external leptin treatment does not provide a significant reduction in body weight and food intake [62]. In obese people, leptin levels increase, but hyperglycemia-correcting or appetite-reducing effects are not observed [63]. Despite the increased leptin levels in obese patients, the absence of the functions of leptin, an appetite-reducing hormone, suggests leptin resistance [64]. It has been suggested that leptin resistance plays a role in the pathogenesis of obesity triggered by overeating [65]. However, the molecular mechanisms underlying leptin resistance have not yet been clearly elucidated. The inability of leptin to cross the blood–brain barrier, inhibition of the intracellular leptin signaling pathway in neurons, and/or downregulation of leptin receptors are thought to be the underlying mechanisms of leptin resistance. It has been reported that a high-fat diet causes an increase in fat mass, leading to hyperleptinemia and triggering leptin resistance [66]. In high-fat rats (*fa/fa*), substitutions in *OB-Rb* result in reduced signaling capacity, leptin binding affinity, and cell surface expression [67]. Obese *fa/fa* rats have leptin resistance and are not sensitive to the effects of leptin. Although obese people may have high plasma leptin concentrations due to leptin resistance, they do not experience the effects of leptin [19].

In gastric chief cells (also known as zymogenic cell or peptic cell), leptin is released upon sensing gastrin and secretin and it is actively inhibited by cholecystokinin [68]. The binding of leptin to its receptor activates the Janus kinase (JAK) signal transducer and activator of the transcription 3 (STAT3) signal transduction pathway, inducing cellular anti-apoptotic events, angiogenesis, and proliferation [69, 70]. The gene product also interacts with IL-1 and Notch cascade, which are involved in promoting tumor growth. Some other pathways activated are mitogen-activated protein kinases/extracellular signal-regulated kinases pathway (MAPK/ERK), phosphatidylinositol 3 kinase (PI3K), 5' AMP activated protein kinase (AMPK), and mTOR [71].

6. Leptin-related cellular pathways

After leptin binds to its receptor on the cell membrane, it acts by stimulating the following signaling pathways in the cell.

6.1 JAK2/ STAT3 signaling pathway

In the activation of this signaling pathway, leptin is activated by phosphorylation of its receptor, binding of STAT3, and phosphorylated by JAK2 [72]. Activated STAT3 enters the nucleus and binds to target sites on DNA; and so cellular activity takes place (**Figure 2**).

Figure 2.

Leptin signaling pathways. POMC; pro-opiomelanocortin, SOCS3; intracellular suppressor of cytokine signal 3, PTP1B; protein tyrosine phosphatase 1B, SHP2; tyrosine phosphatase 2, IRS; (insulin receptor substrate)/PI3K; (phosphoinositol 3 kinase), FoxO1; (forkhead box O1) and mTOR; (mammalian target of rapamycin), S6K; ribosomal S6 kinase, ERK; extracellular signal-regulated kinase [73].

6.2 SHP2/ERK signaling pathway

Stimulation of the leptin receptor activates the protein tyrosine phosphatase 2 (SHP2), contributing to the activation of the ERK signaling pathway, resulting in a cellular response [72, 74].

6.3 JAK2/STAT5 signaling pathway

As a result of the stimulation of the receptor, it provides activation of STAT5 by JAK2. Activated STAT5 acts by binding to the target region in the nucleus [75].

6.4 IRS/ PI3K Signaling pathway

Leptin also activates the IRS (insulin receptor substrate)/PI3K (phosphoinositol 3 kinase) pathway [76, 77] (**Figure 2**). The SH2B1 adapter protein mediates activation of the PI3K pathway by linking the JAK2 and IRS protein via the SH2 domain [78]. In addition, the IRS/PI3K pathway proceeds in two substeps, FoxO1 (forkhead box O1) and mTOR (the mammalian target of rapamycin) (**Figure 2**).

7. The relationship between leptin and oxidative stress

Oxidative stress results from an imbalance between reactive oxygen species (ROS) and the organism's antioxidant defense. Due to oxidative stress, peroxidative damage to macromolecules and membranes of cells occurs in organisms. Moreover, their metabolic activities in cell components are impaired. Known to tissue and organ pathologies occur in the presence of oxidative stress in the organism [79–86]. It has been reported that high leptin levels can induce the formation of ROS, mainly due to nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation [87, 88]. However, leptin replacement therapy has also been shown to significantly downregulate NADPH oxidase expression in AT of leptin-deficient *ob/ob* mice [89]. This indicates that leptin has a protective role at normal levels.

Free radical-mediated peroxidation of membrane lipids loses its integrity, increasing membrane fluidity and permeability. The lipid peroxidation process is one of the oxidative conversions of PUFAs to products known as malondialdehyde (MDA). MDA is a highly toxic molecule and its secondary products such as thiobarbituric acid reactive agent are commonly used to assess lipid peroxidation [90–94]. Glutathione (GSH) is an important nonenzymatic component of the cellular antioxidant system and plays an important role in ROS antioxidation [95–97]. It has been suggested that leptin modulates the activity of various antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) in patients with leptin gene mutations [98]. Leptin production is increased by overexpression of the endogenous antioxidant enzyme catalase and correlates with markers of oxidative stress and inflammatory in *ob/ob* mice [99]. In another study, enzymatic antioxidants including catalase and GSH levels were increased by leptin treatment in *ob/ob* mice, and leptin treatment decreased MDA levels in rats exposed to oxidative stress [100, 101]. It is noted that leptin treatment reverses the effect of streptozotocin (STZ)-induced diabetes by lowering glutathione and catalase levels and increasing lipid peroxidation [102, 103]. It has been reported that defective antioxidant enzyme activity is recovered after leptin treatment in the plasma of humans with leptin gene mutations and *ob/ob* mice [97, 104]. They are most likely the result of the modulatory effect of leptin on metabolic and hormonal disorders. Recombinant leptin treatment leads to weight loss by reducing food intake and has a reducing effect on oxidative stress caused by a high-fat diet [105].

Hyperleptinemia is the most prominent feature of obesity and is likely to be involved in the pathogenesis of obesity-related pathologies [19]. Studies in obese individuals have shown a correlation between leptin levels and oxidative stress parameters such as nitric oxide (NO), superoxide anion (O_2^-), peroxynitrite, MDA, hydroperoxides, protein carbonyl (PC) contents, GSH, and SOD [106–108]. Studies in which hyperleptinemia was induced by the administration of exogenous leptin in nonobese animals suggest that leptin increases the level of systemic oxidative stress [109, 110]. In addition, some *in vitro* studies have shown that in the presence of high leptin concentration, ROS production is stimulated by endothelial cells, inflammatory cells, and other cell types [111–113]. In another *in vitro* study, it was noted that leptin significantly decreased pro-oxidant biomarkers such as MDA and NO and increased antioxidant markers such as total antioxidant capacity (TAC), SOD, and GPx against cryopreservation-induced oxidative stress in rabbit embryos. It has been suggested that leptin can be used as an antiapoptotic and antioxidant promoter to support embryonic development *in vitro* under oxidative stress induced by cryopreservation [114]. In one study, treatment with high glucose caused an increase in oxidative stress in pheochromocytoma (PC12) cells with excessive ROS and MDA production and depletion of GSH content, however, leptin treatment caused a decrease in MDA and ROS levels and an increase in GSH content, resulting in hyperglycemic PC12 cells. It has been reported to significantly reduce the oxidative damage mediated by reactive oxygen species caused by the condition. Therefore, it was stated that leptin may have a protective effect against oxidative stress and apoptosis mediated by reactive oxygen species caused by the hyperglycemic state [115]. In addition, hypothalamic oxidative stress induces leptin resistance, which leads to the induction of insulin resistance and obesity. Activation of nuclear factor erythroid 2-related factor 2 (Nrf2) suppresses hypothalamic oxidative stress and improves leptin resistance in the hypothalamus [116].

8. The relationship between leptin and apoptosis

Recently, some studies have shown that there is an important relationship between leptin and apoptosis; such as in a study, it was determined that there is a

leptin receptor (Ob-R) on the surface of breast cancer cells. Leptin is thought to stimulate these cancer cells with various effects, such as migration and spread. It has been determined that the expression of Ob-R increases as the tumor grows [117]. Another study reported that leptin may affect the risk of breast cancer by increasing estrogen synthesis [118, 119]. It is believed that leptin, which is associated with breast cancer, exerts this effect by affecting the JAK/STAT and MAPK pathways, as well as increasing the transcriptional expression of vascular endothelial growth factor receptor-2 (VEGFR-2) and VEGF [120]. In another study, it was determined that the ratio between leptin and adiponectin is important in regulating the development of breast cancer [121]. Again, in some studies, it has been determined that leptin triggers cell proliferation by stimulating the MAPK pathway in breast cancer cells [122]. It has been observed that leptin also stimulates estrogen receptors via MAPK in breast cancer cells [123].

It has also been reported that leptin is associated with lung cancer. Ob-Ra and Ob-Rb were expressed on the surface of lung cancer cells. It has been determined that leptin plays a role in the development and progression of lung cancer as well as its migration [124, 125]. It has been reported that leptin also increases cytokine production by stimulating JAK/STAT3, PI3K/AKT, and MEK1/2 signaling pathways [126]. In a study, it was determined that the removal of leptin from the medium in non-small cell lung cancer cell lines inactivates the JAK/STAT3 and Notch signaling pathways, thus stopping cell proliferation and stimulating apoptosis (Figure 3) [128].

In some studies, leptin has been shown to stimulate cell proliferation and prevent apoptosis by activation of the PI3K/AKT signaling pathway in thyroid cancer cells [129, 130].

Leptin has been reported to be associated with liver cancer [131]. In one study, they reported elevated leptin levels in patients with hepatocellular carcinoma [132]. It has been determined that leptin increases liver fibrosis by stimulating transforming growth factor- β (TGF- β) synthesis and release. It has also been reported that leptin stimulates the production of a tissue inhibitor of metalloproteinase-1 through the JAK/STAT pathway in hepatic stellate cells [133]. Leptin has also been reported to cause the proliferation of hepatocellular cancer cells by altering cyclin D1, *Bcl-2* (B-cell lymphoma-2)-related X protein (Bax), and apoptotic gene activity [134].

Figure 3. Leptin signaling. AKT; protein kinase B, GRB2; growth factor receptor-bound protein 2, JAK; Janus kinase, Ob-R; leptin receptor, MAPK; mitogen-activated protein kinase, FOS, JUN, JUNB; GENES PI3K; phosphatidylinositol 3 kinase, SHP2; Src homology 2-containing tyrosine phosphatase, STAT3; signal transducer and activator of transcription 3 [127].

Another study demonstrated the presence of leptin receptors on the surface of human colon tumor cells [135]. In colorectal cancer, leptin acts as a very potent mitogen and antiapoptotic cytokine. It has been determined that leptin plays a role in many stages of this type of cancer [136, 137]. It has been reported that leptin increase is proportional to tumor development and tumor metastasis [138]. It has been determined that leptin exerts this effect via JAK and the extracellular signal-regulating kinase (ERK) pathway [139]. In another study, they found that leptin prevented apoptosis and stimulated cell proliferation via PI3K/AKT/mTOR pathways in colon cancer cells (**Figure 4**) [141].

In a study conducted in ovarian cancer, it was determined that leptin is directly related to PI3K/AKT signaling pathways, antiapoptotic proteins XIAP (X-linked inhibitor of apoptosis), and Bcl-XL. By activating these pathways, leptin has been reported to suppress cell proliferation and apoptosis [142]. In another study, it was determined that leptin administration to epithelial ovarian cancer cells increases cancer cell proliferation in a dose-dependent manner, and this increase is done by suppressing genes that inhibit cell proliferation [143].

An increase in leptin levels has been found to be associated with the development of prostate cancer [144]. It has been determined that leptin suppresses apoptosis in prostate cancer cells. Leptin has been reported to exert this effect via the MAPK and PI3K pathways [145]. It has also been reported that leptin stimulates the increase of (hypoxia-inducible factor 1), which is known to play an important role in carcinogenesis in prostate cancer cell culture and stimulates the spread and adhesion of these cells [146].

Figure 4. Intracellular signaling pathways of leptin in connection with cellular proliferation. AKT: Protein kinase B/serine–threonine kinase, ERK: Extracellular signal-regulated kinase, JAK: Janus kinases, MAPK: Mitogen-activated protein kinase, MEK: Mitogen-activated protein kinase, mTOR: Mechanistic/mammalian target of rapamycin, Ob-R: Leptin receptor, PI3K: Phosphatidylinositol3-kinase, STAT: Signal transducer and activator of transcription [140].

9. Conclusion

In conclusion, leptin is adiponectin released from AT. As a result of studies, it has been reported that leptin is associated with oxidative stress and apoptosis, as well as regulating body energy metabolism and food intake. Knowing the release of leptin, its receptor, cellular effects, and especially the relationship between oxidative stress and apoptosis will guide various studies on this subject.

Author details

Volkan Gelen^{1*}, Abdulsamed Kükürt², Emin Şengül³ and Hacı Ahmet Deveci⁴

1 Faculty of Veterinary Medicine, Department of Physiology, Kafkas University, Kars, Turkey

2 Faculty of Veterinary Medicine, Department of Biochemistry, Kafkas University, Kars, Turkey

3 Faculty of Veterinary Medicine, Department of Physiology, Atatürk University, Erzurum, Turkey

4 Faculty of Health Sciences, Department of Nutrition and Dietetics, Gaziantep University, Gaziantep, Turkey

*Address all correspondence to: gelen_volkan@hotmail.com

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet*. 2011;**378**:815-825. DOI: 10.1016/S0140-6736(11)60814-3
- [2] Dhurandhar EJ, Keith SW. The aetiology of obesity beyond eating more and exercising less. *Best Practice & Research. Clinical Gastroenterology*. 2014;**28**:533-544. DOI: 10.1016/j.bpg.2014.07.001
- [3] McAllister EJ, Dhurandhar NV, Keith SW, Aronne LJ, Barger J, Baskin M, et al. Ten putative contributors to the obesity epidemic. *Critical Reviews in Food Science and Nutrition*. 2009;**49**:868-913. DOI: 10.1080/10408390903372599
- [4] Gelen V, Şengül E, Gedikli S, Gür C, Özkanlar S. Therapeutic effect of quercetin on renal function and tissue damage in the obesity induced rats. *Biomedicine & Pharmacotherapy*. 2017;**89**:524-528. DOI: 10.1016/j.biopha.2017.02.057
- [5] Gedikli S, Ozkanlar S, Gur C, Sengul E, Gelen V. Preventive effects of quercetin on liver damages in high-fat diet-induced obesity. *Journal of Histology & Histopathology*. 2017;**4**:7. DOI: 10.7243/2055-091X-4-7
- [6] Koerner A, Kratzsch J, Kiess W. Adipocytokines: leptin—the classical, resistin—the controversial, adiponectin—the promising, and more to come. *Best Practice & Research. Clinical Endocrinology & Metabolism*. 2005;**19**:525-546. DOI: 10.1016/j.beem.2005.07.008
- [7] Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature*. 1998;**395**:763-770. DOI: 10.1038/27376
- [8] Elmquist JK, Elias CF, Saper CB. From lesions to leptin: Hypothalamic control of food intake and body weight. *Neuron*. 1999;**22**:221-232. DOI: 10.1016/S0896-6273(00)81084-3
- [9] Bates SH, Myers MG. The role of leptin receptor signaling in feeding and neuroendocrine function. *Trends in Endocrinology and Metabolism*. 2003;**14**:447-452. DOI: 10.1016/j.tem.2003.10.003
- [10] Zhang F, Chen Y, Heiman M, DiMarchi R. Leptin: Structure, function and biology. *Vitamins and Hormones*. 2005;**71**:345-372. DOI: 10.1016/S0083-6729(05)71012-8
- [11] Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature*. 1997;**387**:903-908. DOI: 10.1038/43185
- [12] Ingalls AM, Dickie MM, Snell GD. Obese, a new mutation in the house mouse*. *Obesity Research*. 1996;**4**:101-101. DOI: 10.1002/j.1550-8528.1996.tb00519.x
- [13] Hummel KP, Dickie MM, Coleman DL. Diabetes, a New Mutation in the Mouse. *Science* (80-). 1966;**153**:1127-1128. DOI: 10.1126/science.153.3740.1127
- [14] Coleman DL. Obese and diabetes: Two mutant genes causing diabetes-obesity syndromes in mice. *Diabetologia*. 1978;**14**:141-148. DOI: 10.1007/BF00429772
- [15] Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature*. 1994;**372**:425-432. DOI: 10.1038/372425a0
- [16] Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, et al.

- Identification and expression cloning of a leptin receptor, OB-R. *Cell*. 1995;**83**: 1263-1271. DOI: 10.1016/0092-8674(95)90151-5
- [17] Gong DW, Bi S, Pratley RE, Weintraub BD. Genomic structure and promoter analysis of the human obese gene. *The Journal of Biological Chemistry*. 1996;**271**:3971-3974. DOI: 10.1074/jbc.271.8.3971
- [18] Ahima RS, Flier JS. Leptin. *Annual Review of Physiology*. 2000;**62**:413-437. DOI: 10.1146/annurev.physiol.62.1.413
- [19] Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, et al. Leptin levels in human and rodent: Measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nature Medicine*. 1995;**1**:1155-1161. DOI: 10.1038/nm1195-1155
- [20] Huising MO, Kruiswijk CP, Flik G. Phylogeny and evolution of class-I helical cytokines. *The Journal of Endocrinology*. 2006;**189**:1-25. DOI: 10.1677/joe.1.06591
- [21] Peelman F, Iserentant H, De Smet AS, Vandekerckhove J, Zabeau L, Tavernier J. Mapping of binding site III in the leptin receptor and modeling of a hexameric leptin-leptin receptor complex. *The Journal of Biological Chemistry*. 2006;**281**:15496-15504. DOI: 10.1074/jbc.M512622200
- [22] Denver RJ, Bonnett RM, Boorse GC. Evolution of leptin structure and function. *Neuroendocrinology*. 2011;**94**:21-38. DOI: 10.1159/000328435
- [23] Al-Suhaimi EA, Shehzad A. Leptin, resistin and visfatin: The missing link between endocrine metabolic disorders and immunity. *European Journal of Medical Research*. 2013;**18**:12-18. DOI: 10.1186/2047-783X-18-12
- [24] Caro JF, Sinha MK, Kolaczynski JW, Zhang PL, Considine RV. Leptin: The tale of an obesity gene. *Diabetes*. 1996;**45**:1455-1462. DOI: 10.2337/diab.45.11.1455
- [25] Inui A. Feeding and body-weight regulation by hypothalamic neuropeptides - Mediation of the actions of leptin. *Trends in Neurosciences*. 1999;**22**:62-67. DOI: 10.1016/S0166-2236(98)01292-2
- [26] Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, et al. Role of leptin in the neuroendocrine response to fasting. *Nature*. 1996;**382**:250-252. DOI: 10.1038/382250a0
- [27] Lutz TA, Woods SC. Overview of animal models of obesity. *Current Protocols in Pharmacology*. 2012. Chapter 5: Unit 5.61. DOI: 10.1002/0471141755.ph0561s58
- [28] Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, et al. Leptin regulates proinflammatory immune responses. *The FASEB Journal*. 1998;**12**:57-65. DOI: 10.1096/fsb2fasebj.12.1.57
- [29] Procaccini C, La Rocca C, Carbone F, De Rosa V, Galgani M, Matarese G. Leptin as immune mediator: Interaction between neuroendocrine and immune system. *Developmental and Comparative Immunology*. 2017;**66**:120-129. DOI: 10.1016/j.dci.2016.06.006
- [30] Dos Santos MA, Pisani LP, Corgosinho FC, Testa Carvalho LO, Masquio DCL, Jamar G, et al. The role of leptinemia state as a mediator of inflammation in obese adults. *Hormone and Metabolic Research*. 2013;**45**:605-610. DOI: 10.1055/s-0033-1343450
- [31] Jéquier E. Leptin signaling, adiposity, and energy balance. *Annals of the New York Academy of Sciences*. 2002;**967**: 379-388. DOI: 10.1111/j.1749-6632.2002.tb04293.x

- [32] Friedman JM. Leptin, leptin receptors, and the control of body weight. *Scandinavian Journal of Nutrition*. 1998;**56**:54-75
- [33] Lönnqvist F, Nordfors L, Jansson M, Thörne A, Schalling M, Arner P. Leptin secretion from adipose tissue in women: Relationship to plasma levels and gene expression. *The Journal of Clinical Investigation*. 1997;**99**:2398-2404. DOI: 10.1172/JCI119422
- [34] Considine RV, Cooksey RC, Williams LB, Fawcett RL, Zhang P, Ambrosius WT, et al. Hexosamines regulate leptin production in human subcutaneous adipocytes. *The Journal of Clinical Endocrinology and Metabolism*. 2000;**85**:3551-3556. DOI: 10.1210/jc.85.10.3551
- [35] Takahashi Y, Ide T. Dietary n-3 fatty acids affect mRNA level of brown adipose tissue uncoupling protein 1, and white adipose tissue leptin and glucose transporter 4 in the rat. *The British Journal of Nutrition*. 2000;**84**:175-184. DOI: 10.1017/s0007114500001409
- [36] Havel PJ, Townsend R, Chaump L, Teff K. High-fat meals reduce 24-h circulating leptin concentrations in women. *Diabetes*. 1999;**48**:334-341. DOI: 10.2337/diabetes.48.2.334
- [37] Havel PJ. Role of adipose tissue in body-weight regulation: Mechanisms regulating leptin production and energy balance. *The Proceedings of the Nutrition Society*. 2000;**59**:256-371. DOI: 10.1017/S0029665100000410
- [38] Heini AF, Lara-Castro C, Schneider H, Kirk KA, Considine RV, Weinsier RL. Effect of hydrolyzed guar fiber on fasting and postprandial satiety and satiety hormones: A double-blind, placebo-controlled trial during controlled weight loss. *International Journal of Obesity*. 1998;**22**:906-909. DOI: 10.1038/sj.ijo.0800680
- [39] Rosenbaum M, Leibel RL. Clinical review 107: Role of gonadal steroids in the sexual dimorphisms in body composition and circulating concentrations of leptin. *The Journal of Clinical Endocrinology and Metabolism*. 1999;**84**:1784-1789. DOI: 10.1210/jcem.84.6.5787
- [40] Ahmed ML, Ong KKL, Morrell DJ, Cox L, Drayer N, Perry L, et al. Longitudinal study of leptin concentrations during puberty: Sex differences and relationship to changes in body composition. *The Journal of Clinical Endocrinology and Metabolism*. 1999;**84**:899-905. DOI: 10.1210/jc.84.3.899
- [41] Hims-Hagen J. Physiological roles of the leptin endocrine system: Differences between mice and humans. *Critical Reviews in Clinical Laboratory Sciences*. 1999;**36**:575-655. DOI: 10.1080/10408369991239259
- [42] Jockenhövel F, Blum WF, Vogel E, Englaro P, Müller-Wieland D, Reinwein D, et al. Testosterone substitution normalizes elevated serum leptin levels in hypogonadal men. *The Journal of Clinical Endocrinology and Metabolism*. 1997;**82**:2510-2513. DOI: 10.1210/jc.82.8.2510
- [43] Kuru M, Ögün M, Kulaksiz R, Kükürt A, Oral H. Comparison of oxidative/nitrosative stress, leptin and progesterone concentrations in pregnant and non-pregnant Abaza goats synchronized with controlled internal drug release application. *Kafkas Universitesi Veteriner Fakultesi Dergisi*. 2018;**24**:887-892. DOI: 10.9775/kvfd.2018.20222
- [44] Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Medicine Reviews*. 2007;**11**:163-178. DOI: 10.1016/j.smrv.2007.01.002
- [45] Bartness TJ, Bamshad M. Innervation of mammalian white

- adipose tissue: Implications for the regulation of total body fat. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*. 1998;**275**:1399-1411. DOI: 10.1152/ajpregu.1998.275.5.r1399
- [46] Hardie LJ, Rayner DV, Holmes S, Trayhurn P. Circulating leptin levels are modulated by fasting, cold exposure and insulin administration in lean but not Zucker (fa/fa) rats as measured by ELISA. *Biochemical and Biophysical Research Communications*. 1996;**223**:660-665. DOI: 10.1006/bbrc.1996.0951
- [47] Eikelis N, Schlaich M, Aggarwal A, Kaye D, Esler M. Interactions between leptin and the human sympathetic nervous system. *Hypertension*. 2003;**41**:1072-1079. DOI: 10.1161/01.HYP.0000066289.17754.49
- [48] Mistry AM, Swick AG, Romsos DR. Leptin rapidly lowers food intake and elevates metabolic rates in lean and ob/ob mice. *The Journal of Nutrition*. 1997;**127**:2065-2072. DOI: 10.1093/jn/127.10.2065
- [49] Lee MJ, Fried SK. Integration of hormonal and nutrient signals that regulate leptin synthesis and secretion. *American Journal of Physiology. Endocrinology and Metabolism*. 2009;**296**:1230-1238. DOI: 10.1152/ajpendo.90927.2008
- [50] Hu Y, Robichaux WG, Mei FC, Kim ER, Wang H, Tong Q, et al. Role of exchange protein directly activated by cyclic AMP Isoform 1 in energy homeostasis: regulation of leptin expression and secretion in white adipose tissue. *Molecular and Cellular Biology*. 2016;**36**:2440-2450. DOI: 10.1128/mcb.01034-15
- [51] Foster-Schubert KE, Cummings DE. Emerging therapeutic strategies for obesity. *Endocrine Reviews*. 2006;**27**:779-793. DOI: 10.1210/er.2006-0041
- [52] Russell CD, Petersen RN, Rao SP, Ricci MR, Prasad A, Zhang Y, et al. Leptin expression in adipose tissue from obese humans: Depot-specific regulation by insulin and dexamethasone. *American Journal of Physiology. Endocrinology and Metabolism*. 1998;**275**:507-515. DOI: 10.1152/ajpendo.1998.275.3.e507
- [53] Elimam A, Knutsson U, Brönnegård M, Stiernä P, Albertsson-Wikland K, Marcus C. Variations in glucocorticoid levels within the physiological range affect plasma leptin levels. *European Journal of Endocrinology*. 1998;**139**:615-620. DOI: 10.1530/eje.0.1390615
- [54] Bradley RL, Cheatham B. Regulation of ob gene expression and leptin secretion by insulin and dexamethasone in rat adipocytes. *Diabetes*. 1999;**48**:272-278. DOI: 10.2337/diabetes.48.2.272
- [55] Laferrère B, Caixas A, Fried SK, Bashore C, Kim J, Pi-Sunyer FX. A pulse of insulin and dexamethasone stimulates serum leptin in fasting human subjects. *European Journal of Endocrinology*. 2002;**146**:839-845. DOI: 10.1530/eje.0.1460839
- [56] Mueller WM, Gregoire FM, Stanhope KL, Mobbs CV, Mizuno TM, Warden CH, et al. Evidence that glucose metabolism regulates leptin secretion from cultured rat adipocytes. *Endocrinology*. 1998;**139**:551-558. DOI: 10.1210/endo.139.2.5716
- [57] Wang J, Liu R, Hawkins M, Barzilal N, Rossetti L. A nutrient-sensing pathway regulates leptin gene expression in muscle and fat. *Nature*. 1998;**393**:684-688. DOI: 10.1038/31474
- [58] Moreno-Aliaga MJ, Stanhope KL, Havel PJ. Transcriptional regulation of the leptin promoter by insulin-stimulated glucose metabolism in 3T3-L1 adipocytes.

Biochemical and Biophysical Research Communications. 2001;**283**:544-548.
 DOI: 10.1006/bbrc.2001.4822

[59] Zhang HH, Kumar S, Barnett AH, Eggo MC. Tumour necrosis factor- α exerts dual effects on human adipose leptin synthesis and release. *Molecular and Cellular Endocrinology*. 2000;**159**: 502-508. DOI: 10.1016/S0303-7207(99)00194-X

[60] Kirchgessner TG, Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Tumor necrosis factor- α contributes to obesity-related hyperleptinemia by regulating leptin release from adipocytes. *The Journal of Clinical Investigation*. 1997;**100**:2777-2782. DOI: 10.1172/JCI119824

[61] Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *The New England Journal of Medicine*. 1996;**334**:292-295. DOI: 10.1056/nejm199602013340503

[62] Halaas JL, Boozer C, Blair-West J, Fidahusein N, Denton DA, Friedman JM. Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. *Proceedings of the National Academy of Sciences of the United States of America*. 1997;**94**:8878-8883. DOI: 10.1073/pnas.94.16.8878

[63] Blüher M. Adipokines - removing road blocks to obesity and diabetes therapy. *Molecular Metabolism*. 2014;**3**:230-240. DOI: 10.1016/j.molmet.2014.01.005

[64] Myers MG, Cowley MA, Münzberg H. Mechanisms of leptin action and leptin resistance. *Annual Review of Physiology*. 2008;**70**:537-556. DOI: 10.1146/annurev.physiol.70.113006.100707

[65] Scarpace PJ, Matheny M, Tümer N, Cheng KY, Zhang Y. Leptin resistance exacerbates diet-induced obesity and is associated with diminished maximal leptin signalling capacity in rats. *Diabetologia*. 2005;**48**:1075-1083. DOI: 10.1007/s00125-005-1763-x

[66] Crujeiras AB, Carreira MC, Cabia B, Andrade S, Amil M, Casanueva FF. Leptin resistance in obesity: An epigenetic landscape. *Life Sciences*. 2015;**140**:57-63. DOI: 10.1016/j.lfs.2015.05.003

[67] Da Silva BA, Bjørbæk C, Uotani S, Flier JS. Functional properties of leptin receptor isoforms containing the gln $\rightarrow$ pro extracellular domain mutation of the fatty rat. *Endocrinology*. 1998;**139**:3681-3690. DOI: 10.1210/endo.139.9.6168

[68] Mix H, Manns MP, Wagner S, Widjaja A, Jandl O, Cornberg M, et al. Expression of leptin and leptin receptor isoforms in the human stomach. *Gut*. 2000;**47**:e7624. DOI: 10.1136/gut.47.4.481

[69] Triantafyllou GA, Paschou SA, Mantzoros CS. Leptin and hormones: Energy homeostasis. *Endocrinology and Metabolism Clinics of North America*. 2016;**45**:633-645. DOI: 10.1016/j.ecl.2016.04.012

[70] Mullen M, Gonzalez-Perez RR. Leptin-induced JAK/STAT signaling and cancer growth. *Vaccine*. 2016;**4**:26. DOI: 10.3390/vaccines4030026

[71] Park HK, Ahima RS. Leptin signaling. *F1000Prime Reports*. 2014;**6**:73. DOI: 10.12703/P6-73

[72] Banks AS, Davis SM, Bates SH, Myers MG. Activation of downstream signals by the long form of the leptin receptor. *The Journal of Biological Chemistry*. 2000;**275**:14563-14572. DOI: 10.1074/jbc.275.19.14563

[73] Zhou Y, Rui L. Leptin signaling and leptin resistance. *Frontiers in Medicine*.

2013;7:207-222. DOI: 10.1007/s11684-013-0263-5

[74] Bjørnbæk C, Lavery HJ, Bates SH, Olson RK, Davis SM, Flier JS, et al. SOCS3 mediates feedback inhibition of the leptin receptor via Tyr985. *The Journal of Biological Chemistry*. 2000;275:40649-40657. DOI: 10.1074/jbc.M007577200

[75] Gong Y, Ishida-Takahashi R, Villanueva EC, Fingar DC, Münzberg H, Myers MG. The long form of the leptin receptor regulates STAT5 and ribosomal protein S6 via alternate mechanisms. *The Journal of Biological Chemistry*. 2007;282:31019-31027. DOI: 10.1074/jbc.M702838200

[76] Xu AW, Kaelin CB, Takeda K, Akira S, Schwartz MW, Barsh GS. PI3K integrates the action of insulin and leptin on hypothalamic neurons. *The Journal of Clinical Investigation*. 2005;115:951-958. DOI: 10.1172/JCI200524301

[77] Morris DL, Rui L. Recent advances in understanding leptin signaling and leptin resistance. *American Journal of Physiology-Endocrinology and Metabolism*. 2009;297:E1247-E1259. DOI: 10.1152/ajpendo.00274.2009

[78] Duan C, Li M, Rui L. SH2-B Promotes Insulin Receptor Substrate 1 (IRS1)- and IRS2-mediated Activation of the Phosphatidylinositol 3-Kinase Pathway in Response to Leptin. *The Journal of Biological Chemistry*. 2004;279:43684-43691. DOI: 10.1074/jbc.M408495200

[79] Gelen V, Kükürt A, Şengül E, Başer ÖF, Karapehlivan M. Can polyphenols be used as anti-inflammatory agents against Covid-19 (SARS-CoV-2)-induced inflammation? In: Badria FA, editor. *Phenolic Compd. [Working Title]*. Rijeka: IntechOpen; 2021. pp. 1-21. DOI: 10.5772/intechopen.98684

[80] Kükürt A, Kuru M, Karapehlivan M. Nitrik oksit, nitrik oksit sentaz ve dişi

üreme sistemindeki rolleri. In: Evereklioglu C, editor. *Sağlık Bilim. Alanında Akad. Çalışmalar - II, Gece Kitaplığı*. Ankara: Gece Publishing; 2020. pp. 113-123

[81] Gelen V, Kükürt A, Şengül E. Role of the renin-angiotensin-aldosterone system in various disease processes: An overview. In: *Renin-Angiotensin Aldosterone Syst. [Working Title]*. Rijeka: IntechOpen; 2021. DOI: 10.5772/intechopen.97354

[82] Kükürt A. Doğal bir antioksidan olarak propolis tedavisinin koruyucu etkileri. In: Evereklioglu C, editor. *Sağlık Bilim. Teor. ve Araştırmalar II, Gece Kitaplığı*. Ankara: Gece Publishing; 2020. pp. 501-515

[83] Kükürt A, Kuru M, Faruk Başer Ö, Karapehlivan M. Kisspeptin: Role in female infertility. In: Marsh C, editor. *Reprod. Horm. Rijeka: IntechOpen; 2021. DOI: 10.5772/intechopen.94925*

[84] Başer ÖF, Kükürt A, Karapehlivan M. Oksidatif stresin azaltılmasında anjiyotensin dönüştürücü enzimin rolü. In: Evereklioglu C, editor. *Sağlık Bilim. Teor. ve Araştırmalar II, Gece Kitaplığı*. Ankara: Gece Publishing; 2020. pp. 243-253

[85] Kükürt A, Gelen V, Faruk Başer Ö, Ahmet Deveci H, Karapehlivan M. Thiols: Role in oxidative stress-related disorders. In: *Lipid Peroxidation [Working Title]*. Rijeka: IntechOpen; 2021. DOI: 10.5772/intechopen.96682

[86] Kara A, Gedikli S, Sengul E, Gelen V, Ozkanlar S. Oxidative stress and autophagy. In: *Free Radicals Disease. Rijeka: InTech; 2016. DOI: 10.5772/64569*

[87] Morawietz H, Bornstein SR. Leptin, endothelin, NADPH oxidase, and heart failure. *Hypertension*. 2006;47:20-21. DOI: 10.1161/01.HYP.0000218452.18010.fb

- [88] Dong F, Zhang X, Ren J. Leptin regulates cardiomyocyte contractile function through endothelin-1 receptor–NADPH oxidase pathway. *Hypertension*. 2006;**47**:222-229. DOI: 10.1161/01.HYP.0000198555.51645.f1
- [89] Frühbeck G, Catalán V, Rodríguez A, Ramírez B, Becerril S, Portincasa P, et al. Normalization of adiponectin concentrations by leptin replacement in ob/ob mice is accompanied by reductions in systemic oxidative stress and inflammation. *Scientific Reports*. 2017;**7**:2752. DOI: 10.1038/s41598-017-02848-0
- [90] Niki E, Yoshida Y, Saito Y, Noguchi N. Lipid peroxidation: Mechanisms, inhibition, and biological effects. *Biochemical and Biophysical Research Communications*. 2005;**338**:668-676. DOI: 10.1016/j.bbrc.2005.08.072
- [91] Gelen V, Şengül E. Antioxidant, anti-inflammatory and antiapoptotic effects of naringin on cardiac damage induced by cisplatin. *Indian Journal of Traditional Knowledge*. 2020; **19**:459-465
- [92] Gelen V, Sengul E, Yildirim S, Celebi F, Cinar A. Effects of rutin on bladder contractility and histopathology in cyclophosphamide-induced hemorrhagic cystitis in rats. *Atatürk University Journal of Veterinary Sciences*. 2018;**13**:337-346
- [93] Karamese M, Guvendi B, Karamese SA, Cinar I, Can S, Erol HS, et al. The protective effects of epigallocatechin gallate on lipopolysaccharide-induced hepatotoxicity: An in vitro study on Hep3B cells. *Iranian Journal of Basic Medical Sciences*. 2016;**19**:483-489
- [94] Sengul E, Gelen V, Yildirim S, Tekin S, Dag Y. The effects of selenium in acrylamide-induced nephrotoxicity in rats: Roles of oxidative stress, inflammation, apoptosis, and DNA damage. *Biological Trace Element Research*. 2021;**199**:173-184
- [95] Gelen V, Şengül E, Yildirim S, Senturk E, Tekin S, Kükürt A. The protective effects of hesperidin and curcumin on 5-fluorouracil-induced nephrotoxicity in mice. *Environmental Science and Pollution Research*. 2021;**34**:47046-47055. DOI: 10.1007/s11356-021-13969-5
- [96] Sengul E, Gelen V, Gedikli S. Cardioprotective activities of quercetin and rutin in sprague dawley rats treated with 5-fluorouracil. *Journal of Animal and Plant Sciences*. 2020;**31**:423-431
- [97] Şengül E, Gelen V, Gedikli S, Özkanlar S, Gür C, Çelebi F, et al. The protective effect of quercetin on cyclophosphamide-Induced lung toxicity in rats. *Biomedicine & Pharmacotherapy*. 2017;**92**:303-307. DOI: 10.1016/j.biopha.2017.05.047
- [98] Ozata M, Uckaya G, Aydin A, Isimer A, Ozdemir IC. Defective antioxidant defense system in patients with a human leptin gene mutation. *Hormone and Metabolic Research*. 2000;**32**:269-272. DOI: 10.1055/s-2007-978634
- [99] Amos DL, Robinson T, Massie MB, Cook C, Hoffsted A, Crain C, et al. Catalase overexpression modulates metabolic parameters in a new ‘stress-less’ leptin-deficient mouse model. *Biochimica et Biophysica Acta, Molecular Basis of Disease*. 2017;**1863**:2293-2306. DOI: 10.1016/j.bbdis.2017.06.016
- [100] Erkasap S, Erkasap N, Koken T, Kahraman A, Uzuner K, Yazihan N, et al. Effect of leptin on renal ischemia-reperfusion damage in rats. *Journal of Physiology and Biochemistry*. 2004; **60**:79-84. DOI: 10.1007/BF03168443
- [101] Zwirska-Korczala K, Adamczyk-Sowa M, Sowa P, Pilc K,

- Suchanek R, Pierzchala K, et al. Role of leptin, ghrelin, angiotensin II and orexins in 3T3 L1 preadipocyte cells proliferation and oxidative metabolism. *Journal of Physiology and Pharmacology*. 2007;**58**:53-64
- [102] Madhkhoo SR, Ibrahim IR. Evaluation of some stress indicators and their relation with leptin injection in experimentally induced diabetic rats. *International Journal of Advanced Research*. 2016;**4**:9-13. DOI: 10.21474/IJAR01/102
- [103] Gülen Ş, Dinçer S. Effects of leptin on oxidative stress in healthy and Streptozotocin-induced diabetic rats. *Molecular and Cellular Biochemistry*. 2007;**302**:59-65. DOI: 10.1007/s11010-007-9426-5
- [104] Watson AM, Poloyac SM, Howard G, Blouin RA. Effect of leptin on cytochrome P-450, conjugation, and antioxidant enzymes in the ob/ob mouse. *Drug Metabolism and Disposition*. 1999;**27**:695-700
- [105] Sailaja JBK, Balasubramaniyan V, Nalini N. Effect of exogenous leptin administration on high fat diet induced oxidative stress. *Pharmazie*. 2004;**59**: 475-479
- [106] Essa Ahmed S, Maher FT, Ahmed NN. Effect of leptin and oxidative stress in the blood of obese individuals. *Biochemistry and Analytical Biochemistry*. 2016;**5**:3. DOI: 10.4172/2161-1009.1000288
- [107] Malti N, Merzouk H, Bouhmama L, Saker M, Elhabiri M, Cherrak S. Time course of changes in leptin levels and their relationships with oxidant status biomarkers in pregnant women with obesity. *Journal of Clinical and Diagnostic Research*. 2020;**14**:1-5. DOI: 10.7860/JCDR/2020/43475.13640
- [108] Ali IMM, Yenzeel JH, Al-ansari HMS. Evaluation of oxidative stress and leptin level in samples of Iraqi obese women. *Iraqi Journal of Science*. 2020;**61**:1565-1570. DOI: 10.24996/ijs.2020.61.7.3
- [109] Beltowski J, Wójcicka G, Jamroz A. Leptin decreases plasma paraoxonase 1 (PON1) activity and induces oxidative stress: the possible novel mechanism for proatherogenic effect of chronic hyperleptinemia. *Atherosclerosis*. 2003;**170**:21-29. DOI: 10.1016/S0021-9150(03)00236-3
- [110] Beltowski J, Wójcicka G, Marciniak A, Jamroz A. Oxidative stress, nitric oxide production, and renal sodium handling in leptin-induced hypertension. *Life Sciences*. 2004;**74**: 2987-3000. DOI: 10.1016/j.lfs.2003.10.029
- [111] Maingrette F, Renier G. Leptin increases lipoprotein lipase secretion by macrophages: Involvement of oxidative stress and protein kinase C. *Diabetes*. 2003;**52**:2121-2128. DOI: 10.2337/diabetes.52.8.2121
- [112] Bouloumié A, Marumo T, Lafontan M, Busse R. Leptin induces oxidative stress in human endothelial cells. *The FASEB Journal*. 1999;**13**:1231-1238. DOI: 10.1096/fasebj.13.10.1231
- [113] Savini I, Catani MV, Rossi A, Duranti G, Ranalli M, Melino G, et al. Vitamin C recycling is enhanced in the adaptive response to leptin-induced oxidative stress in keratinocytes. *The Journal of Investigative Dermatology*. 2003;**121**:786-793. DOI: 10.1046/j.1523-1747.2003.12538.x
- [114] Alshaheen TA, Awaad MHH, Mehaisen GMK. Leptin improves the in vitro development of preimplantation rabbit embryos under oxidative stress of cryopreservation. *PLoS One*. 2021;**16**: e0246307. DOI: 10.1371/journal.pone.0246307
- [115] Kaeidi A, Hajializadeh Z, Jahandari F, Fatemi I. Leptin attenuates

- oxidative stress and neuronal apoptosis in hyperglycemic condition. *Fundamental & Clinical Pharmacology*. 2019;**33**:75-83. DOI: 10.1111/fcp.12411
- [116] Yagishita Y, Uruno A, Fukutomi T, Saito R, Saigusa D, Pi J, et al. Nrf2 improves leptin and insulin resistance provoked by hypothalamic oxidative stress. *Cell Reports*. 2017;**18**:2030-2044. DOI: 10.1016/j.celrep.2017.01.064
- [117] Surmacz E. Leptin and adiponectin: Emerging therapeutic targets in breast cancer. *Journal of Mammary Gland Biology and Neoplasia*. 2013;**18**:321-332. DOI: 10.1007/s10911-013-9302-8
- [118] Jardé T, Caldefie-Chézet F, Goncalves-Mendes N, Mishellany F, Buechler C, Penault-Llorca F, et al. Involvement of adiponectin and leptin in breast cancer: Clinical and in vitro studies. *Endocrine-Related Cancer*. 2009;**16**:1197-1210. DOI: 10.1677/ERC-09-0043
- [119] Khan S, Shukla S, Sinha S, Meeran SM. Role of adipokines and cytokines in obesity-associated breast cancer: Therapeutic targets. *Cytokine & Growth Factor Reviews*. 2013;**24**:503-513. DOI: 10.1016/j.cytogfr.2013.10.001
- [120] Gonzalez-Perez R, Lanier V, Newman G. Leptin's Pro-Angiogenic Signature in Breast Cancer. *Cancers (Basel)*. 2013;**5**:1140-1162. DOI: 10.3390/cancers5031140
- [121] Ray A. Adipokine leptin in obesity-related pathology of breast cancer. *Journal of Biosciences*. 2012;**37**:289-294. DOI: 10.1007/s12038-012-9191-9
- [122] Laud K, Gourdou I, Pessemesse L, Peyrat JP, Djiane J. Identification of leptin receptors in human breast cancer: functional activity in the T47-D breast cancer cell line. *Molecular and Cellular Endocrinology*. 2002;**188**:219-226. DOI: 10.1016/S0303-7207(01)00678-5
- [123] Catalano S, Mauro L, Marsico S, Giordano C, Rizza P, Rago V, et al. Leptin Induces, via ERK1/ERK2 Signal, Functional Activation of Estrogen Receptor α in MCF-7 Cells. *The Journal of Biological Chemistry*. 2004;**279**:19908-19915. DOI: 10.1074/jbc.M313191200
- [124] Bruno A, Siena L, Gerbino S, Ferraro M, Chanez P, Giammanco M, et al. Apigenin affects leptin/leptin receptor pathway and induces cell apoptosis in lung adenocarcinoma cell line. *European Journal of Cancer*. 2011;**47**:2042-2051. DOI: 10.1016/j.ejca.2011.03.034
- [125] Song C-H, Liao J, Deng Z-H, Zhang J-Y, Xue H, Li Y-M, et al. Is leptin a predictive factor in patients with lung cancer? *Clinical Biochemistry*. 2014;**47**:230-232. DOI: 10.1016/j.clinbiochem.2013.12.003
- [126] Shen Y, Wang Q, Zhao Q, Zhou J. Leptin promotes the immune escape of lung cancer by inducing proinflammatory cytokines and resistance to apoptosis. *Molecular Medicine Reports*. 2009;**2**:295-299. DOI: 10.3892/mmr_00000099
- [127] Andò S, Catalano S. The multifactorial role of leptin in driving the breast cancer microenvironment. *Nature Reviews. Endocrinology*. 2012;**8**:263-275. DOI: 10.1038/nrendo.2011.184
- [128] Zheng X-J, Yang Z-X, Dong Y-J, Zhang G-Y, Sun M-F, An X-K, et al. Downregulation of leptin inhibits growth and induces apoptosis of lung cancer cells via the Notch and JAK/STAT3 signaling pathways. *Biology Open*. 2016;**5**:794-800. DOI: 10.1242/bio.017798
- [129] Uddin S, Bavi P, Siraj AK, Ahmed M, Al-Rasheed M, Hussain AR, et al. Leptin-R and its association with PI3K/AKT signaling pathway in

- papillary thyroid carcinoma.
- Endocrine-Related Cancer*
- . 2010;
- 17**
- :191-202. DOI: 10.1677/ERC-09-0153
- [130] Uddin S, Hussain AR, Siraj AK, Khan OS, Bavi PP, Al-Kuraya KS. Role of leptin and its receptors in the pathogenesis of thyroid cancer. *International Journal of Clinical and Experimental Pathology*. 2011;**4**:637-643
- [131] Ribatti D, Belloni AS, Nico B, Di Comite M, Crivellato E, Vacca A. Leptin–leptin receptor are involved in angiogenesis in human hepatocellular carcinoma. *Peptides*. 2008;**29**:1596-1602. DOI: 10.1016/j.peptides.2008.05.011
- [132] Miyahara K, Nouse K, Tomoda T, Kobayashi S, Hagihara H, Kuwaki K, et al. Predicting the treatment effect of sorafenib using serum angiogenesis markers in patients with hepatocellular carcinoma. *Journal of Gastroenterology and Hepatology*. 2011;**26**:1604-1611. DOI: 10.1111/j.1440-1746.2011.06887.x
- [133] Duan X-F, Tang P, Li Q, Yu Z-T. Obesity, adipokines and hepatocellular carcinoma. *International Journal of Cancer*. 2013;**133**:1776-1783. DOI: 10.1002/ijc.28105
- [134] Cheung OK-W, Cheng AS-L. Gender differences in adipocyte metabolism and liver cancer progression. *Frontiers in Genetics*. 2016;**7**:5-6. DOI: 10.3389/fgene.2016.00168
- [135] Stattin P, Lukanova A, Biessy C, Söderberg S, Palmqvist R, Kaaks R, et al. Obesity and colon cancer: Does leptin provide a link? *International Journal of Cancer*. 2004;**109**:149-152. DOI: 10.1002/ijc.11668
- [136] Pietrzyk L, Torres A, Maciejewski R, Torres K. Obesity and obese-related chronic low-grade inflammation in promotion of colorectal cancer development. *Asian Pacific Journal of Cancer Prevention*. 2015;**16**:4161-4168. DOI: 10.7314/APJCP.2015.16.10.4161
- [137] Riondino S. Obesity and colorectal cancer: Role of adipokines in tumor initiation and progression. *World Journal of Gastroenterology*. 2014;**20**:5177. DOI: 10.3748/wjg.v20.i18.5177
- [138] Tutino V, Notarnicola M, Guerra V, Lorusso D, Caruso MG. Increased soluble leptin receptor levels are associated with advanced tumor stage in colorectal cancer patients. *Anticancer Research*. 2011;**31**:3381-3383
- [139] Yoon K-W, Park S-Y, Kim J-Y, Lee S-M, Park C-H, Cho S-B, et al. Leptin-induced adhesion and invasion in colorectal cancer cell lines. *Oncology Reports*. 2014;**31**:2493-2498. DOI: 10.3892/or.2014.3128
- [140] Ray A, Fornasaglio J, Dogan S, Hedau S, Naik D, De A. Gynaecological cancers and leptin: A focus on the endometrium and ovary. *Facts, Views & Vision in ObGyn*. 2018;**10**:5-18
- [141] Wang D, Chen J, Chen H, Duan Z, Xu Q, Wei M, et al. Leptin regulates proliferation and apoptosis of colorectal carcinoma through PI3K/Akt/mTOR signalling pathway. *Journal of Biosciences*. 2012;**37**:91-101. DOI: 10.1007/s12038-011-9172-4
- [142] Uddin S, Bu R, Ahmed M, Abubaker J, Al-Dayel F, Bavi P, et al. Overexpression of leptin receptor predicts an unfavorable outcome in Middle Eastern ovarian cancer. *Molecular Cancer*. 2009;**8**:74. DOI: 10.1186/1476-4598-8-74
- [143] Ptak A, Kolaczowska E, Gregoraszczuk EL. Leptin stimulation of cell cycle and inhibition of apoptosis

gene and protein expression in
OVCAR-3 ovarian cancer cells.
Endocrine. 2013;**43**:394-403. DOI:
10.1007/s12020-012-9788-7

[144] Alshaker H, Sacco K, Alfraidi A,
Muhammad A, Winkler M,
Pchejetski D. Leptin signalling, obesity
and prostate cancer: Molecular and
clinical perspective on the old dilemma.
Oncotarget. 2015;**6**:35556-35563. DOI:
10.18632/oncotarget.5574

[145] Osório CF, Souza DB de,
Gallo CBM, Costa WS, Sampaio FJB.
Leptin and leptin receptor expressions
in prostate tumors may predict disease
aggressiveness? Acta Cirúrgica Brasileira
2014;**29**:44-48. 10.1590/
S0102-86502014001700009.

[146] Calgani A, Delle Monache S,
Cesare P, Vicentini C, Bologna M,
Angelucci A. Leptin contributes to
long-term stabilization of HIF-1 α in
cancer cells subjected to oxygen limiting
conditions. Cancer Letters. 2016;**376**:1-
9. DOI: 10.1016/j.canlet.2016.03.027