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New Perspectives on Obesity Related Novel Peptides

Obeziteyle İlişkili Güncel Peptitlere Yeni Yaklaşımlar

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ÖZ

Özellikle çocukluk ve adölesan zamanlarında gelişen obezite, her yaşta önemli bir sağlık sorunu olarak karşımıza çıkmaktadır. Hipotalamusu vücudun enerji depoları hakkında uyaran hormonlar, yemek yemeyi engelleyip vücut ağırlığının belli fizyolojik sınırlar içerisinde kalmasını sağlamaktadırlar. Obezite ve obeziteyle ilişkili olan hormonların araştırılması bu kapsamda çok önemlidir. Obezite ile ilişkili hormonların günümüze kadar tespit edilmiş olan fonksiyonlarının, daha ileri çalışmalara rehberlik edebileceğini düşünmekteyiz. Bu derlemede obeziteyle ilişkili hormonlar ve onların etki mekanizmalarına değinilmiştir.

Anahtar Kelimeler: ghrelin; irisin; leptin; nesfatin-1; nöropeptid-y; oreksin

ABSTRACT

Obesity, which develops especially in childhood and adolescence, is an important health problem at all ages. Hormones that stimulate the hypothalamus about the body's energy stores prevent eating and keep body weight within certain physiological limits. Investigating obesity and the hormones associated with obesity is very important in this context. We believe that the functions of obesity-associated hormones that have been identified to date can guide further studies. In this review, obesity-related hormones and their mechanisms of action are discussed.

Keywords: ghrelin; irisin; leptin; nesfatin-1; neuropeptide-y; orexin

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OBESITY

Obesity is a chronic condition which may lead to physical, psychological, social, and economic problems caused by the excess of energy received with nutrients over the energy expended.[1] Obesity has recently started to be a common health problem in all societies and has shown a rapid increase in all age periods, starting from childhood and adolescence in many countries.[2] On the other hand, body fat mass, which is the increase of body weight above the desired level regarding height as a result of an excessive increase in the ratio of desired mass, is closely related to adipose tissue. It is well known that another factor that attracts attention in the progress of the obesity is dependent on the way of nutrition in the first years of the life of people. In a study conducted on breastfed and non-breastfed children, the rate of obesity was found to be lower in breastfed children. In addition, this study emphasized that the duration of breastfeeding, the type and number of complementary foods, and the time of onset affect the occurrence of obesity.[3] Obesity, which is an epidemic problem, directly affects the development of many chronic diseases. Also obesity is directly related with the diseases e.g., type 2 DM hypertension, coronary heart, metabolic diseases, respiratory system diseases and cancer.[4]

When we analyze the biochemistry of nutrition, the first definitions that come to mind are peptides that regulate food intake. According to their origin, these peptides are classified as peptides produced in the CNS and peripheral peptides produced in the digestive tract. According to their effects on nutritional behavior, they are grouped as orexigenic and anorexigenic peptides. Orexigenic peptides stimulate food intake by initiating the feeling of hunger, while anorexigenics are peptides that stop food intake by creating a feeling of satiety (table 1).[5]

Table 1. Some known orexigenic and anorexigenic peptides.[5]

OREXIGENIC PEPTIDES	ANOREXIGENIC PEPTIDES
Ghrelin	Leptin
Noropeptit y (NPY)	Insulin
Arcuate-associated peptide (AGRP)	Glucagon-like peptide-1 (GLP-1)
Melanin concentrating hormone (MCH)	Cholecystokinin (CCK)
Orexin	Cocaine amphetamine regulatory transcript (CART)
Galanin	α-Melanocyte stimulating hormone (α - MSH)
Opioids	Serotonin
Nitric oxide *	Corticotropin-releasing factor (CRF)
Kannabioits *	Nesfatin- 1
	Bombesin

* A peptide is an element that is not in the structure.

HORMONES INVOLVED IN OBESITY

LEPTIN

Leptin discovered in 1994 is an important appetite-regulating hormone with a molecular weight 16 kDa and a single-chain polypeptide structure encoded by the LEP (OB) gene located on the long part of the chromosome (7q31)which is a protein product with 167 amino acids. Leptin is formed by white/brown adipose tissue, the placenta, stomach, mammary gland, ovarian follicles, heart, bone/cartilage tissue, some fetal organs, and the brain. Leptin reduces the intake of nutrients and increases the metabolic rate. It is believed that leptin shows this effect via inhibiting the synthesis of NPY, AgRP (Agouti-related peptide) and MSH which are released from the arcuate nucleus (Bound leptin reflects the energy state at rest, and free leptin reflects the body fat mass (figure1-2).[5]

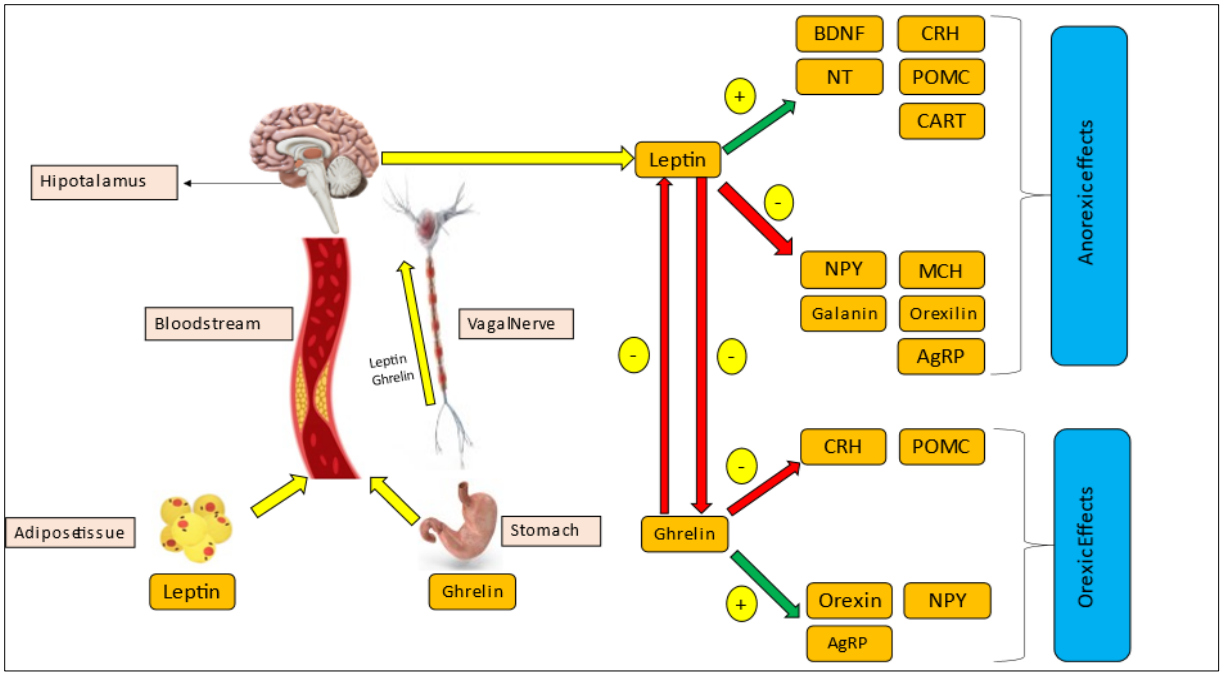

Figure 1. The physiological mechanism of leptin action.

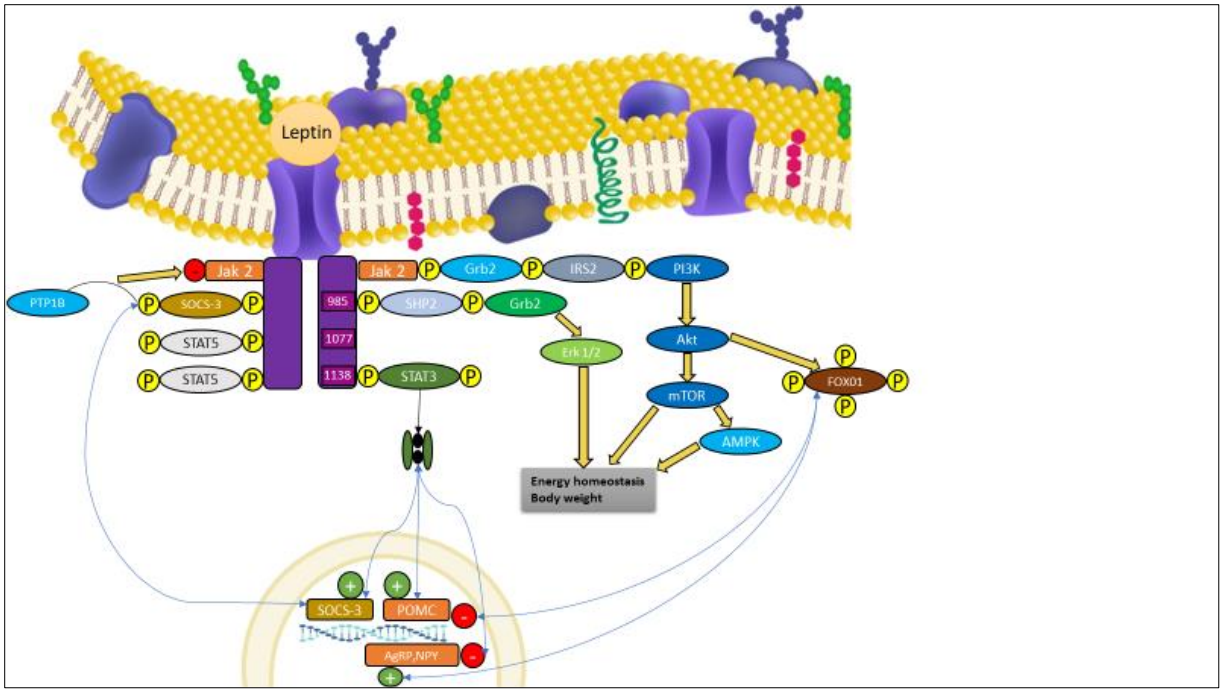

Figure 2. Leptin signaling pathway overview.

The expression of proopiomelanocortin (POMC) is induced in hypothalamic leptin, and AgRP and NPY are inhibited. Thus, these changes increase releasing of gonadotropin-releasing hormones (GnRH), thyrotropin (TRH). Leptin reduces the release of ACTH, and CRH, and inhibits insulin secretion from pancreatic β-cells.[6]

Leptin crosses the blood-brain barrier with a special active transport system. In an obese person, leptin levels in the cerebrospinal fluid are less high than their circulating amount.[7] In addition, in the absence of leptin or mild leptin fluctuations, the arcuate nucleus, paraventricular nucleus, lateral and dorsomedial hypothalamic neuronal connections of the hypothalamus are inhibited. Therefore, it causes metabolic complications and leads to obesity. There are findings that obesity caused by leptin deficiency in humans, decreased the number of circulating $CD4^{(+)}$ T cells,

impaired T cell receptor immunity, and the release of cytokine can be adjusted by recombinant leptin applications.[8]

GHRELIN

Ghrelin was extracted from the stomach by Kojima and colleagues in 1999. It is a hormone containing 28 amino acids in structure and has been identified as an endogenous ligand of the type 1a receptor. It forms the active form of ghrelin, that also provides the release of growth hormone by binding an n-octenyl group fatty acid to serine which is the 3rd amino acid of ghrelin. This form is called active or acyl ghrelin.[9]

Ghrelin shows its effect by binding to GHS-R type 1a. By binding to the receptor, it induces the secretion of growth hormone-releasing hormone (GHRH) in the hypothalamus.[10]

Anorexigenic activation of ghrelin is regulated by neurons that engage specific receptors in the hypothalamus. Ghrelin is a regulator that has very different effects on metabolism. Ghrelin is found in hypothalamic neurons that regulate satiety and food intake. At the same time, ghrelin receptors are also present in other neurons that contribute to eating behavior in brain regions. While this increases ghrelin levels, it causes a decrease in leptin levels. This state can result in obesity. NPY gene expressions stimulated and increased by ghrelin eliminate the decreases in food intake induced by leptin. On the contrary, inhibition of NPY gene expressions causes suppression of food intake mediated by leptin and is the main mechanism. Amphetamine (AMPH), is used for the treatment of obesity, was determined to be used in obese individuals for appetite suppression.[11]

NEUROPEPTIDE Y, PEPTIDE YY AND PANCREATIC POLYPEPTIDE (PP)

Neuropeptide Y (NPY), peptide YY (PYY), pancreatic polypeptide (PP) and peptide Y (PY) polypeptides are members of the Neuropeptide Y peptide family. Among them, NPY is a peptide with 36 amino acids, which is widely found in the central and peripheral nervous system along with AgRP. NPY is found mostly in the sympathetic nerves, and fewer in parasympathetic nerves. NPY blood flow rate as well as metabolic rate decreases in brown adipose tissue. The Y5 receptor, one of the five G-protein receptors of neuropeptide Y, appears to be definitively responsible for regulating food intake.[5]

NPY influences adipose tissue apart from the effect of hypothalamic NPY on food intake,.Central NPY injection causes an increase in adipose tissue by increasing the level of plasma corticosterone and insulin.[12] The level of both insulin and leptin increases with an increase in adipose tissue. The synthesis and activity of NPY are inhibited. Thus, nutrient intake is reduced. Conversely, with food restriction (for example, when insulin or leptin levels are too low in the fasting state), the level of NPY increases. As a result, an increase in food intake occurs. The physiological role of NPY in nutrition, which is the most important effect, has not been fully determined due to the complexity of the common effects of NPY on the hypothalamus. When this receptor is precisely determined, it will be quite important in the cure of obesity. The synthesis of PYY and PP is carried out only by endocrine cells in the digestive tract. NPY in the intestinal–brain and brain–intestinal axis also existed. NPY and PYY alter digestive system motility and entry to the brain through inhibition of electrolyte secretion. PYY is also affected by the gut microbiota. NPY have a pro-inflammatory effect by stimulating Y1 receptors. PP and PYY send signals to the brain. They reduce appetite, anxiety and depression in this way. The information given above shows that NPY, PYY and PP have a significant role of the NPY-Y receptor system at various grade of the intestinal–brain axis as both neural and endocrine messengers.[13]

PYY in the intestine is produced by endocrine L cells. These cells are abundant in the lower gastrointestinal tract.[14] PYY L cells contain glicentin, glucagon-like peptide-1 and glucagon-like peptide-2, a proglucagon-derived peptide.[15] It is thought that L cells containing PYY are important chemo sensors in the intestine.[16]

The function of NPY, PYY and PP is associated with the expression of different Y receptor subtypes. After eating, PP is released from the pancreas and exerts its tue via the Y4 and Y5 receptors. This mechanism of action affecting the vagus nerve prevents gastric emptying. The decrease

in appetite through vagal signaling is caused by this effect.[17] PP also has an inhibitory role on intestinal motor activity and peristalsis. This newly discovered role in glucose homeostasis makes PYY an important one for the treatment of diabetes and obesity.[13]

NESFATIN-1

Nesfatin-1, first discovered by Shimizu et al.[18] in 2006, is a neurohormone or satiety molecule derived from the nucleobindin 2 [nucleobindin 2 (NUCB2)] protein that is expressed in humans and rats, especially in the hypothalamus, adipose tissue, pancreas, gastric mucosa, and brain. Nesfatin-1, which is newly discovered and identified as one of the anorexigenic peptides, affects the centers of the brain by targeting the arcuate nucleus where the hunger and satiety regions are located in the hypothalamus or by reaching the tractus solitarius nucleus in the brainstem and crossing the blood-brain barrier with a neural network interaction.[19] Nesfatin-1 is a receptor-sensitive amino-terminal fragment activated by a peroxisome proliferator consisting of 82 amino acids (MW 9.7 kDa). As a result of the translation of NUCB2, a protein consisting of 396 amino acids is released. NUCB2, which can be divided post-translationally by the pro-hormone converting enzyme, ultimately forms three different peptide products (segments). These segments are N-terminal nesfatin-1 (amino acid 1-82), nesfatin-2 (amino acid 85-163) and C-terminal nesfatin-3 (amino acid 166-396).[19] It is synthesized from nucleobindin 2 (NUCB2), known as the satiety peptide. Besides the effects of nesfatin-1 in the nervous system, it also has roles on the appetite mechanism and nutritional status.[18] Nesfatin-1 is closely related to diabetes, obesity. It is also associated with anorexia nervosa, psychiatric disorders and neurogenic diseases (figure3).[20]

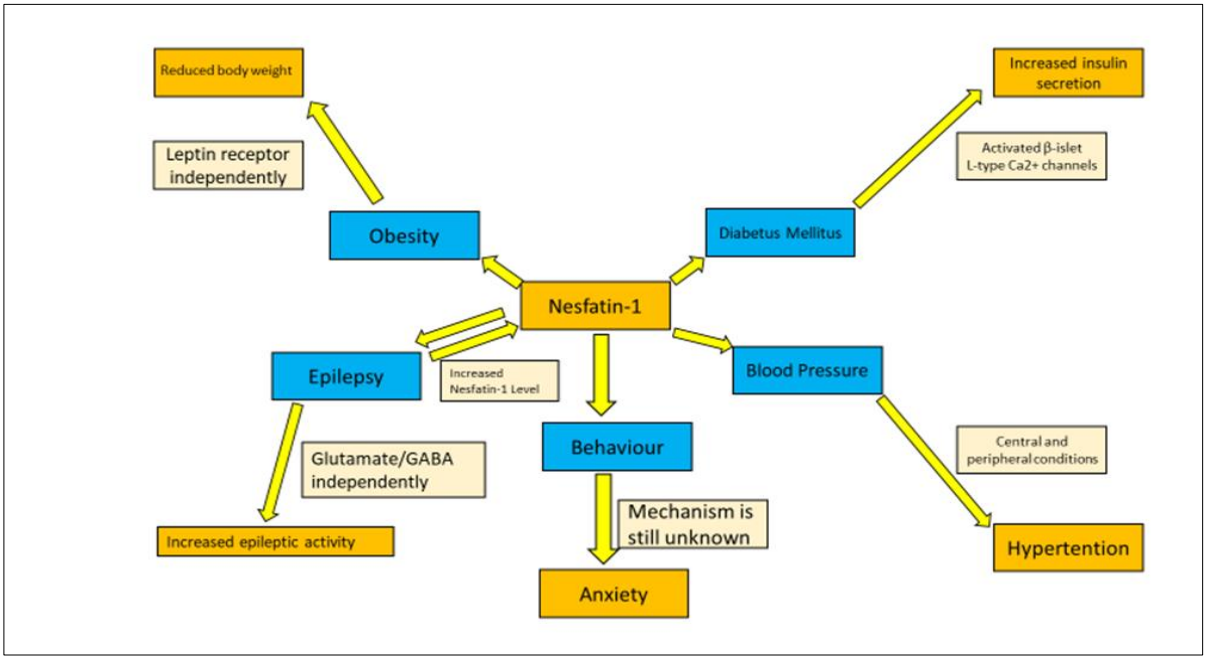

Figure 3. Common clinical state of Nesfatin-1.

In a study, it was reported that nesfatin-1 and NUCB2 levels increased 2 hours after feeding in 48 hours of fasting of rats.[21] This shows that nesfatin-1 plays a role in the regulation of energy balance, especially after eating. Nesfatin-1 is effective in the physiological control of nutrition. By suppressing the peristalsis of the digestive system, it reduces food intake. It plays a role in controlling body weight.[18] Chronic infusion of Nesfatin-1 is reported to steadily inhibit body weight gain and reduce white adipose tissue.[19] In another rat study, nesfatin-1 decrease food intake, feeding frequency on a dose-dependent basis (0.3 nmol).[20] All the data obtained show that Nesfatin-1 is an anorexigenic signaling agent. It has been found that serum nesfatin-1 is less in obese individuals. In a study which is performed on polycystic ovary syndrome (PCOS) women (n=55) showed that serum nesfatin -1 levels are negatively related with body mass index (BMI) Besides, congenital nesfatin-1 enzyme deficiency is associated with obesity.[22]

OREXIN

Orexin A contains 33 amino acids, while orexin B contains 28 amino acids. The similarity of amino acid sequence of orexin B is to 46% of orexin A.[23] Although the pharmacodynamics effects of orexin A and orexin B are relatively similar, their pharmacokinetic properties differ. Orexin A, due to its high lipophilic property, quickly enters the brain by passive diffusion. Orexin B, on the other hand, cannot enter the brain due to its low lipophilic property and is rapidly metabolized in the blood.[24] Nakabayashi et al.[25] showed that mRNA expression for pre-pro-orexin has been identified in kidney, adrenal gland, pancreas, placenta, stomach, ileum, colon and colorectal epithelial cells. This result shows that the production of orexin A also occurs in human peripheral tissues. Orexins are in the endocrine cells of the pancreas, but its functional significance has not been clearly defined.It has been suggested that orexin-A stimulates glucose uptake in adipocytes, increases lipogenesis by inhibiting hormone-sensitive lipase, and in addition to these effects, it inhibits the activation of peroxisome proliferator activated receptor gamma (PPARγ), which controls immune and inflammatory responses.[26] In addition to their triggering effects on food intake, orexins have been found to be involved in various hypothalamic control mechanisms with their effects on the continuation of wakefulness, neuroendocrine, cardiovascular and cognitive functions. Orexins synthesized by neurons located in the hypothalamus have been reported to exert neuroendocrine effects both in the hypothalamus and on the pituitary gland.[27]

It is stated that the role of orexin in energy balance is realized by inhibiting anorexinergic arcuate neurons and activating orexinergic arcuate neurons in contrast.[28] In a conducted study, there is no clear knowledge about whether orexin causes hyperphagia by directly affecting the systems in the appetite regulation or by affecting other neuropeptides. Some experts note that orexins do not cause obesity, despite the effect of increasing food intake. The reason for this state, orexins also increase metabolic rate. In a study, it postulated that orexin neurons inhibit leptin receptors, while leptin given to rats reduces the level of hypothalamic orexin A and reduces the activity of orexin neurons.[28] The results of studies show that orexin-A can act as a hormone-like substance. It does this by regulating the effects of insulin on food and glucose. Besides, there is evidence that orexin-A and leptin play a regulatory role in rodent's feeding behavior. Chronic intraperitoneal leptin administration has a weight loss effect.At the same time, a significant decrease in the orexin-A mRNA levels of the hypothalamus also occurs with this application.[29]

IRISIN

Irisin, was identified by Pontus et al.[30] in 2012, is a peptide protein consisting of 112 amino acids. Irisin is a myokine which is the proteolytic product of fibronectin type III domain 5 (FNDC5), a membrane protein in muscles.[31] It causes an increase in brown adipose tissue. Thus, it causes an increase in energy consumption. It also mediates the positive effects of exercise on metabolism.[20] It is produced in skeletal muscle and adipose tissue, heart tissue, intracranial arteries, kidney, myelin sheath, neural cells, ovaries, Purkinje cells, rectum, salivary glands, sweat glands, stomach, testes, and tongue tissues.[32]

Peroxisome proliferators are stimulated because of exercise, which leads to energy expenditure. This causes the activation of the receptor gamma (PPARy) and PGC1-A. This activation causes an increase in the expression of the FNDC5 gene. PGC1-α controls the mitochondrial biogenesis and oxidative energy metabolism of many cells as an intermediary. FNDC5 is synthesized and secreted from the muscle tissue via PGC1-α, and it regulates the gene expression of brown adipose tissue mitochondrial protein 1 (UCP1), cytochrome c oxidase 7a (COX7a) and otopetrin 1 (OTOP1). 20 nm FNDC5 added to the adipose tissue culture medium increased UCP1 expression by about 7 ratios. Increased expression of UCP1 inhibits ATP synthesis. It leads to the formation of heat. It causes energy expenditure. FNDC5 regulates thermogenesis in brown adipose tissue (figure 4).[20]

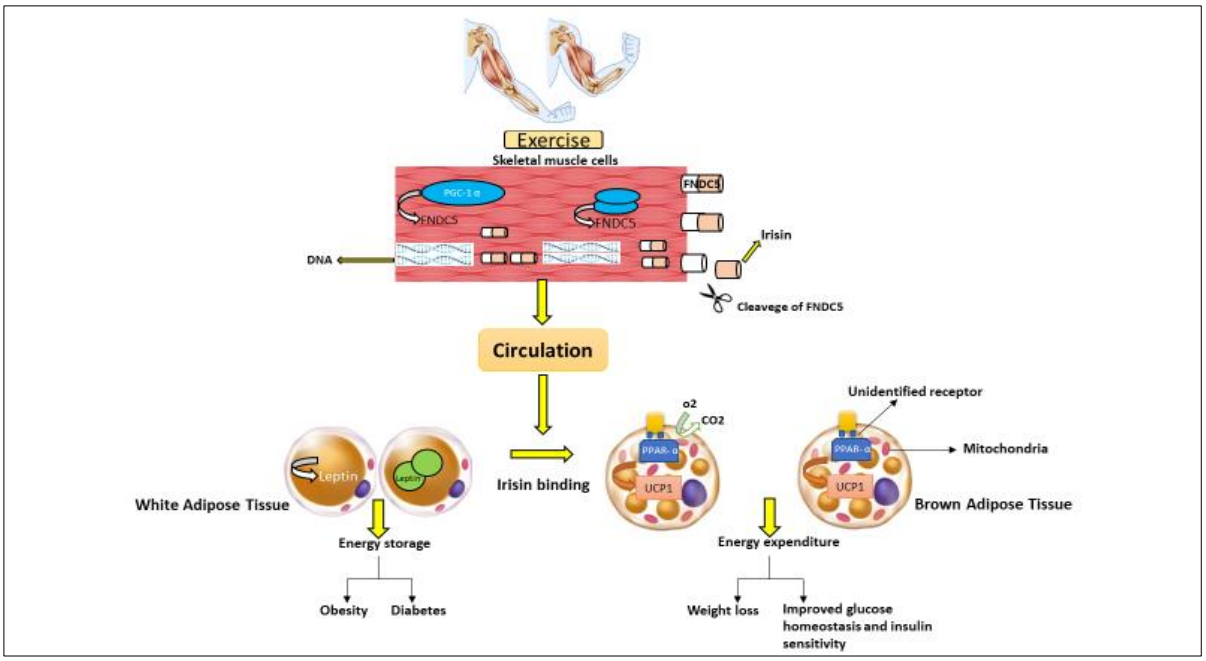

Figure 4. Exercise-induced browning of adipose tissue with irisin and PGC-1α.

Irisin which is firstly investigated in skeletal muscle, is synthesized, and secreted in many tissues. Even though there are contrary results in the studies, it is stated that irisin has many physiological properties in such as weight loss, decreasing in insulin resistance, is related with obesity, glucose regulation, and effects on lipid metabolism.[31] Although irisin is prominent with its myokine identity secreted from muscle, it is an adipokine due to its secretion from adipose tissue. When the effect of circulating irisin levels was examined, the secretion from white adipose tissue was at a lower level than that secreted from muscle.[33]

Despite studies showing that irisin levels decrease when adipose tissue increases, the level of circulating irisin increases when waist circumference and waist/hip ratio and leptin levels increase. Individuals with the normal range of BMI is and without any metabolic disorders, the majority of circulating irisin levels are secreted from muscle cells, while in obese individuals the amount of irisin is secreted because of an increase in body fat mass is excessive in adipose tissue.[33] It is believed that significantly reducing irisin levels in the blood and FNDC5 gene expression in obese people who have lost body weight by bariatric surgery method supports that mechanisms for reducing high irisin levels in obese people may be a therapeutic approach. But in a study that clarified the insulin level after bariatric surgery in obese individuals, it was also determined that the level of irisin increased in response to decreased body mass (figure 4).[31]Again, a lower irisin level in the elderly obese group is associated with age-related decreased muscle function. In obesity, the synthesis of circulating irisin levels increases as a regulatory response to the metabolic disorders such as low insulin levels and insulin resistance. The high level of irisin in obesity may benefit as a predictive factor in use for early diagnosis and treatment. Physical activity, which is very important in controlling metabolic problems such as obesity, Type 2 DM, cardiovascular diseases, is also associated with the hormone irisin that increases because of muscle contraction. In relation to the exercise performed, the levels of iris in the tissues vary.[34] In studies with long-term exercise plans, an increase in blood irisin levels is increases immediately after daily training, while a slowly decreases is observed after 30 minutes. There is no difference in circulating irisin levels after the end of the planned exercise study. Therefore, it can be concluded the acute effective elevation of the blood irisin level during exercises is due to the fact of homeostatic regulation of ATP and followed by a decrease in basal concentrations.[35]

It is believed that irisin has an important role in decrease the amount of fat in the body, since it is a thermogenic agent.[36] In previous research, irisin levels were found to be 353.1±18.6 ng/mL in obese individuals and 198.4±7.8 ng/mL in controls. Irisin were measured as 353.1±18.6

ng/mL in men and 267.6±12 ng/mL in women. This study shows that irisin levels are higher in men in relation to gender.[36] Circulating irisin increases in obesity as a compensatory response to hyperglycemia. at the same time, it has been suggested that the sensitivity of the iris to insulin and leptin decreases.[37]

An association between plasma iris concentrations of the obese and diabetic group and body mass index, age and different biochemical parameters could not be determined. Also, when all Type 2 diabetes patients were grouped separately, it was found that there was an association between circulating irisin levels and both HbA1c and urea.[38]

AMYLIN

Amylin is a polypeptide consisting of 37 Amino acids. In case of satiety, insulin is secreted from the β cells of the pancreas as a signal of satiety. It exerts its effect by acting on cortical homeostatic and hedonic brain regions. It prolongs the emptying process of the stomach and suppresses the secretion of glucagon. It plays a primary role in regulating glucose levels after childbirth by creating an anorectic signal. Therefore, synthetic amylin analogues can take part in the treatment process of obese individuals as anti-obesity drugs.[39]

Amylin plays an important role in regulating post-meal satiety. It activates proopiomelanocortin neurons through amylin kinase signaling. This pathway is regulated by extracellular signaling. This arrangement is made independently of leptin.[40] It seems that amylin will be very useful for losing weight and regulating glucose levels. Due to the short duration of action of amylin and its tendency to self-cluster, it makes it difficult to show the above-mentioned effects for a long time.[41]

The use of analogues of amylin in the treatment of obesity seems to be a reliable option that increases the likelihood of obtaining results. It is stated that administration of amylin analogues in combination with GLP-1 (glucagon such as peptide-1) agonists for more weight loss is more beneficial compared to monotherapy. For these therapeutic agents to be used effectively in the treatment of obesity, conducting studies in which more examples are included is important in terms of effectiveness and reliability.[42]

OBESTATIN

Injection of a newly discovered hormone, obestatin, prolongs the residence time of food in the stomach. It is revealed in new studies that the feeding and contraction stimuli of the ghrelin hormone on the jejunal muscles are reduced by obestatin.[43] It is stated that obestatin prevents thirst, strengthens memory and affects sleep. In addition, it is stated that it positively affects cell proliferation, release of pancreatic enzymes, survival, and inhibits the stimulation of insulin release by glucose.[44]

In a study conducted on rats that underwent gastrectomy, it was found that obestatin and ghrelin levels decreased by 50-80%.[45] Anorexigenic effects have been found to occur in rats after the first peripheral or intracerebroventricular injection of obestatin.[43,46] In some recent studies, it is stated that Obestatin has no inhibitory effect on food intake and weight gain.[47] Lagaud et al.[46] demonstrated the effects of obestatin on the diet of rats at different dose ranges. Treatment with obestatin for a period of 7 days was found to suppress food intake and weight gain in rodents.[46]

PREPTIN

Isolated from the beta cells of the rat Pancreas in 2001, the amount of preptin in circulation is halved in less than five minutes. An increase or decrease in its level is closely related to insulin levels in humans. Preptin-stimulated Insulin secretion has been found to be at a similar level to glibenclamide in mice.[49]

It is revealed in the above study that preptin and amylin are produced at the same time by the beta cells of the pancreas. Infusion of preptin into isolated and perfused rat pancreas increases glucose-mediated insulin secretion by 30% in the second phase. It is reported that antipreptin immunoglobulin infusion reduces first phase secretion by 29% and second phase secretion by 26%.[50] Preptin levels were found to be higher in patients with diabetes mellitus than in healthy individuals. In addition, a positive correlation was observed between diastolic blood pressure, triglyceride, total cholesterol, HbA1c and HOMA-IR index and plasma preptin concentrations.[48]

In a study, preptin levels in serum and fetal cord blood of 31 pregnant women of the same age with and without gestational diabetes were investigated. Preptin levels were found to be higher in the maternal serum and fetal cord blood of the diabetic group. A positive correlation was found between preptin levels and maternal age, fasting insulin level, blood glucose level in the first hour after sugar loading, and fetal cord preptin.[50]

Conclusion

As a result of a study conducted on obese individuals who received nutrition and exercise training, it was found that irisin levels did not change, but there was a moderate correlation between plasma irisin levels and HOMA-IR levels. In this way, it was determined that adiponectin showed anti-obesity property.

Hormones that inform the hypothalamus about the body's energy stores prevent eating and ensure that body weight remains within certain physiological limits. It is very crucial to clarify obesity, which has emerged as an increasing health problem in recent years, and hormones related to obesity. In this context, we conclude that the functions of obesity-related hormones mentioned above will guide further studies.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Ethics Committee Permission

Since the study is a compilation, ethics committee permission is not required.

Authors' Contributions

Concept/Design: SK, EM. Literature Search: SK, LS. Drafting manuscript: SK, LS, EM. Critical revision of manuscript: EM, LS. Supervisor: EM.

REFERENCES

1. Aktaş D, Öztürk FN, Kapan Y. Adölesanlarda obezite sıklığı ve etkileyen risk faktörleri, beslenme alışkanlıklarının belirlenmesi. TAF Prev. Med. Bull. 2015;14(5):406-412.
2. Aysoydan E, Çakır N. Adölesanların beslenme alışkanlıkları, fiziksel aktivite düzeyleri ve vücut kitle indekslerinin değerlendirilmesi. Gulhane Med J. 2011; 53(4):264-270.
3. Ergül Ş, Kalkım A. Önemli bir kronik hastalık: çocukluk ve ergenlik döneminde obezite. TAF Prev. Med. Bull. 2011;10(2):223-230.
4. Uskun E, Öztürk M, Kişioğlu A, Kirbiyik S, Demirel R. İlköğretim öğrencilerinde obezite gelişimini etkileyen. SDÜ Tıp Fak Derg. 2005;12(2):19-25.
5. Hızlı H, Büyükuslu N. Yüksek yağlı diyetin açlıktokluk metabolizmasında görevli hormonlar ve nöropeptidler üzerine etkileri. Saglik Bilim. Derg. 2018; 27(3):239-344.
6. Zhang F, Chen Y, Heiman M, DiMarchi R. Leptin: structure, function, and biology. Vitam. Horm. 2005;71:345-372.
7. Öztürk AS, Arpacı A. Obezite ve Ghrelin/Leptin ilişkisi. Mustafa Kemal univ. tıp derg. 2018;9(35): 136-151.
8. Yura S, Itoh H, Sagawa N. et al. Role of premature leptin surge in obesity resulting from intrauterine undernutrition. Cell metabolism. 2005;1(6):371-378.
9. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999; 402(6762):656-660.
10. McKee KK, Palyha OC, Feighner SD, et al. Molecular analysis of rat pituitary and hypothalamic growth hormone secretagogue receptors. Mol. Endocrinol. 1997; 11(4):415-423.
11. Schmid SM, Hallschmid M, Jauch-chara K, Born J, Schultes B. A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. J. Sleep Res. 2008;17(3): 331-334.
12. Wyss P, Stricker-Krongrad A, Brunner L, et al. The pharmacology of neuropeptide Y (NPY) receptor-mediated feeding in rats characterizes better Y5 than Y1, but not Y2 or Y4 subtypes. Regul. Pept. 1998;75:363-371.
13. Holzer P, Reichmann F, Farzi A. Neuropeptide Y, peptide YY and pancreatic polypeptide in the gut–brain axis. Neuropeptides. 2012;46(6):261-274.
14. Ueno H, Yamaguchi H, Mizuta M, Nakazato M. The role of PYY in feeding regulation. Regul. Pept. 2008;145(1-3):12-16.
15. Cox HM. Neuropeptide Y receptors; antisecretory control of intestinal epithelial function. Auton. Neurosci. 2007;133(1):76-85.
16. Rozengurt N, Wu SV, Chen MC, Huang C, Sternini C, Rozengurt E. Colocalisation of the a subunit of gustducin with PYY and GLP-1 in L-cells of human colon. Am. J. Physiol. 2006;291(5):792-802.
17. Murphy KG, Bloom SR. Gut hormones and the regulation of energy homeostasis. Nature. 2006;444(7121): 854-859.
18. Shimizu H, Oh IS, Satoh T, et al. Identification of nesfatin-1 as a satiety molecule in the hypothalamus. Nature. 2006;443(7112):709-712.
19. İşgüzar Y, Akbulut G. Obezite ile ilgili güncel iki hormon: Nesfatin-I ve Omentin-I. Türkiye Klinikleri J Health Sci. 2019;4(1):57-61.
20. Gülmez C, Atakişi O. Yeni hormonlar: R-Spondin-1, Nesfatin-1 ve İrisin. Caucasian Med J. 2019;6(1):37-50.
21. Daisuke K, Mascroni N, Yuko M, Hiroyuki S, Udual S, Natsu Y. Nesfatin 1 neurons in paraventricular and supraoptic nuclei of the rat hypothalamus coexpress oxytocin and vasopressin anda re activated by. Endocrinology. 2008;149(3):1295-1301.
22. Abaci A, Catli G, Anik A, Kume T, Bober E. The relation of serum nesfatin-1 level with metabolic and clinical parameters in obese and healthy children. Pediatr. Diabetes. 2013;14(3):189-195.

23. Lees G, Coyne L. The orexins: a novel family of sleep regulating neuropeptides. CACC 2004;15(1):75-77.
24. Mondal MS, Nakazato M, Matsukura S. Orexins (hypocretins): novel hypothalamic peptides with divergent functions. Biochem. Cell Biol. 2000;78(3): 299-305.
25. Nakabayashi M, Suzuki T, Takahashi K, et al. Orexin-A expression in human peripheral tissues. Mol. Cell. Endocrinol. 2003;205(1-2):43-50.
26. Bülbül A, Tülüceoğlu EE, Öztürk Ö, Calapoğlu NŞ, Gonca T, Calapoğlu M. Serum oreksin seviyelerinin obezite ile ilişkisi: kesitsel ilişkilendirme çalışması. SDÜ Tıp Fak Derg. 2018;9(4):37-43.
27. Yurtseven DG, Minbay Z, Eyigör Ö. Nesfatin-1 ve Oeksin A nöronları arasındaki etkileşimin immünohistokimyasal olarak araştırılması. UÜTFD. 2019; 45(3):243-249.
28. Karadağ MG, Aksoy M. Yeni keşif nöropeptitlerden: Oreksin.GTD.2009;24(2):79-87.
29. Beck B, Richy S, Hypothalamic hypocretin/orexin, and neuropeptide Y: divergent interaction with energy depletion and leptin. Biochem. Biophys. Res. Commun. 1999;258(1):119-122.
30. Pontus B, Jun W, Mark PJ at all. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012:481(7382): 463-810.
31. Sarioğlu B. İrisin hormonu. Sağlık ve Toplum. 2021; 31(3):59-66.
32. Aydın SF. Three new players in energy regulation: preptin, adropin and irisin. Peptides. 2014;56:94-110.
33. Crujeiras AB, Zulet MA, Lopez LP, et al. Association between circulating irisin levels and the promotion of insulin resistance during the weight maintenance period after a dietary weight-lowering program in obese patients. Metabolism. 2014;63(4):520-531.
34. Martinez Munoz IY, Camarillo Romero EdS, Garduno Garcia JdJ. Irisin a novel metabolic biomarker: present knowledge and future directions. Int. J. Endocrinol. 2018:7816806.
35. Huh JY, Mougios V, Skraparlis A, Kabasakalis A, Mantzoros CS. Irisin in response to acute and chronic whole-body vibration exercise in humans. Metabolism. 2014;63(7):918-921.
36. Boström P, Wu J, Jedrychowski MP, et al. A PGC1- -dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012; 481(7382):463-468.
37. Montez JM, Soukas A, Asilmaz E, Fayzikhodjaeva G, Fantuzzi G, Friedman JM. Acute leptin deficiency, leptin resistance, and the physiologic response to leptin withdrawal. Proc Natl Acad Sci. 2005;102(7): 2537-2542.
38. Sanchis-Gomar F, Lippi G, Mayero S, Perez-Quilis C, García-Giménez JL. Irisin: a new potential hormonal target for the treatment of obesity and type 2 diabetes. J Diabetes. 2012;4(3):196-196.
39. Ogawa A, Harris V, McCorkle SK, Unger RH, Luskey KL. Amylin secretion from the rat pancreas and its selective loss after streptozotocin treatment. J Clin Invest. 1990;85(3):973-976.
40. Boccia L, Gamakharia S, Coester B, Whiting L, Lutz TA, Le Foll C. Amylin brain circuitry. Peptides 2020; 132:170366.
41. Qiu WQ, Zhu H. Amylin and its analogs: a friend or foe for the treatment of Alzheimer's disease? Front Aging Neurosci. 2014;6:186.
42. Babak D, Nicholas RSS, Carel WR. Amylin as a future obesity treatment. J Obes Metab Syndr. 2021;30(4): 320-325.
43. Zhang JV, Ren PG, Avsian-Kretchmer O, et al. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. Science. 2005; 310(5750):996-999.
44. Ren AJ, Guo ZF, Wang YK, et al. Inhibitory effect of obestatin on glucose-induced insulin secretion in rats. Biochem Biophys Res Commun. 2008;369(3):969-972.
45. Furnes WM, Stenstro¨m B, Tømmera˚ s K, et al. Feeding behaviour in rats subjected to gastrectomy or gastric bypass surgery. Eur Surg Res. 2008;40(3):279-288.
46. Lagaud GJ, Young A, Acena A, Morton MF, Barrett TD, Shankley NP. Obestatin reduces food intake and suppresses body weight gain in rodents. Biochem Biophys Res Commun. 2007;357(1):264-269.
47. Sibilia V, Bresciani E, Lattuada N, et al. Intracerebroventricular acute and chronic administration of obestatin minimally affect food intake but not weight gain in the rat. J Endocrinol Invest. 2006;29:31-34.
48. Yang GY, Li L, Chen WW, Liu H, Boden G, Li K. Circulating preptin levels in normal, impaired glucose tolerance, and type 2 diabetic subjects. Ann Med. 2009;41(1):52-56.
49. Cheng KC, Li YX, Asakawa A, et al. Characterization of preptin-induced insulin secretion in pancreatic-cells. J Endocrinol. 2012;215(1):43-49.
50. Aslan M, Celik O, Karsavuran N, et al. Maternal serum, and cord blood preptin levels in gestational diabetes mellitus. J Perinatol. 2011;31(5):350-355.