UDC 616.43–056.52:616.092.9
DOI:10.54503/0514-7484-2024-64.2-45

The Peripheral and Central Effects of Reward-Associated Adipokines

H. S. Harutyunyan

Department of Biochemistry, COBRAIN Center,
Yerevan State Medical University after M. Heratsi
2 Koryun Str., 0025, Yerevan, Armenia

Keywords: adipokines, obesity, brain reward system, leptin, adiponectin, hunger, satiety

Introduction

Obesity has notably increased in the last few decades, associated with a disbalance in diet, overconsumption of calories, artificial additions, hypodynamic lifestyle, etc. [1]. Increased adipose tissue mass is a major cause of low-rate chronic inflammation [15].

Adipose tissue was long considered a storage for triglycerides, hence recently with the massive increase in obesity rate, it has been approved as a large endocrine gland implicated in several aspects of hunger and satiety regulation. Adipose tissue produces a wide variety of pro- and anti-inflammatory adipokines. Altered production or release of adipokines leads to disbalance in hunger and satiety mechanisms, which is tightly associated with obesity and its complications. Among these insulin and leptin resistance, hormonal dysbalance, and overload with the musculoskeletal system, cause pain and discomfort [6].

The reward system is a brain network comprising a mesolimbic dopaminergic system and interconnected cortical and subcortical structures. Among the main functions of the reward system are mediating a feeling of pleasure from expecting and receiving a reward, motivation, reward-associated learning, thus adapting to the environment, predicting reward and aversion, etc. [2]. According to the latest research, dysfunction in the reward system is among the major causes of uncontrollable eating, leading to overweight and obesity [20].

Interestingly, adipokines are major players in regulating reward circuits. Many of them such as leptin, adiponectin, and resistin have receptors in homeostatic and hedonic areas of the brain [33]. As the mass of adipose tissue increases, the production and release of adipokines are altered, hence leading to the impaired functioning of reward circuits, causing overeating, anhedonia, neuroinflammation, causing loss of the neurons [24].

This work aims to review the central effects of reward-associated adipokines in the development of obesity.

Role of adipokines in energy balance

Adipose tissue is heterogenic and is composed of adipocytes, stem cells, fibroblasts, vascular cells, macrophages, and T cells. The oxygen supply is maintained through a dense network of blood vessels [7]. Adipocytes primarily store fat as a long-term energy source, hence recently their role as endocrine system regulators was highlighted. Adipokines are hormones or hormone-like compounds, which are largely involved in maintaining a balance between food consumption and energy expenditure [41]. Adipose tissue produces several adipokines, some of which are represented below:

Leptin is considered a satiety hormone and is involved in the regulation of appetite and energy balance [12]. Leptin signals the brain about the amount of fat stores and its level under normal physiological conditions corresponds to the fat stores [31]. Leptin receptors are found in areas of the brain responsible for homeostatic and hedonic aspects of food intake. Leptin production, transport, and signaling impairments are observed in obesity [11].

Adiponectin is involved in the regulation of the level of glucose, as well as the oxidation of fatty acids. It has well-expressed anti-inflammatory properties and improves insulin sensitivity [16]. Altered levels of adiponectin are associated with impairments in reward processing, causing psychiatric conditions, such as depression, addiction, and mood disorders. Adiponectin receptors were identified in the areas responsible for reward processing [36].

Resistin is a pro-inflammatory adipokine. High levels of resistin contribute to insulin resistance and inflammation, metabolic disorders, and impairments in glucose metabolism [3]. Resistin receptors were identified in the brain areas responsible for homeostatic and hedonic food intake, suggesting the possible effect of resistin on brain areas [43].

Visfatin, also known as nicotinamide phosphoribosyltransferase (NAMPT) is a modulator for glucose metabolism and inflammation [46]. It increases insulin sensitivity and was identified as a potential insulin-mimetic, due to its ability to bind to the insulin receptor and facilitate glucose intake by adipocytes. Visfatin is also synthesized by skeletal muscles and the liver. Visfatin contributes to NAD^+ biosynthesis, involved in energy metabolism, repair system, antioxidant protection, and stress response [9].

Apelin exerts its effects through APJ receptors. It is implicated in fluid homeostasis, cardiovascular regulation, and normal maintenance of metabolism. Regulates blood pressure and cardiovascular health, modulating the effects of angiotensin II [17].

Chemerin is involved in the differentiation of adipose stem cells into adipocytes – adipogenesis and regulates the immune system. It acts as a chemoattractant recruiting inflammatory cells to the inflammation sites and modulating inflammatory responses. It is also involved in glucose and lipid metabolism and contributes to insulin sensitivity [37].

Omentin facilitates anti-inflammatory responses and improves insulin sensitivity [38]. It has well-expressed antioxidant, anti-inflammatory, anti-atherosclerotic, anti-tumor, and anti-apoptotic functions [47]. It is a metabolic regulator and improves cardiovascular health [26].

Fibroblast growth factor 21 (FGF21) is involved in the regulation of glucose and lipid metabolism [28]. It affects energy expenditure and may affect insulin sensitivity [26].

The interplay of adipokines contributes to the maintenance of homeostasis of the organism's energy balance and physiological environment.

Peripheral and central effects of reward-associated adipokines

Some adipokine receptors are expressed in homeostatic and hedonic areas of the brain, suggesting the possible involvement of adipokines in energetic metabolism and modulation of reward pathways.

Leptin: In healthy-weight individuals, food consumption holds a dynamic balance with energy expenditure. Leptin is among the adipokines substantially involved in the regulation of this process [39]. It is synthesized primarily from the adipose tissue and “informs” higher brain centers about the amount of the fat stored. Obese individuals were found to have higher leptin levels, compared to lean people [44]. Leptin has a wide distribution of Ob-R receptors in the central nervous system and in the periphery, hence homeostatic and hedonic aspects of leptin are exerted when it binds to its receptors in the hypothalamus and reward pathways. On the hypothalamic level, leptin has a wide density of receptors in the hypothalamic arcuate nucleus and has a key role in regulating appetite and balance of the calories consumed and energy expended. Outside the hypothalamus, leptin receptors were found in the hippocampus, nucleus accumbens, amygdala, and cortex [34].

After a meal, in response to the increased glucose, insulin is released into the blood. On the level of adipose tissue, insulin contributes to the synthesis of fat [14]. It has long been proposed that insulin has a direct effect on leptin production, hence these data were not approved. It was found that insulin levels are in positive correlation with blood levels of leptin. It was proposed that insulin may affect the release of leptin from the adipose tissue. In the blood, leptin crosses the blood-brain and binds to its receptors primarily in the arcuate nucleus of the hypothalamus [40].

Arcuate nucleus has two major subpopulations of neurons, implicated in hunger and satiety regulation: proopiomelanocortin (POMC) / Cocaine-amphetamine regulated transcript (CART) expressing neurons, which exert anorexigenic effect, suppressing appetite and inducing feeling of satiety and Neuropeptide Y (NPY) and Agouti-related Protein (AgRP) expressing neurons, which exert orexigenic effect, inducing appetite and feeding behaviour [30]. Central injection of POMC processing products, such as α-melanocyte

stimulating hormone and NPY or AgRP will suppress and induce food intake correspondingly. Genetic deletion of POMC leads to severe obese phenotype [25]. Deletion of leptin receptors also leads to the expression of obese phenotype, hence it is milder compared with POMC [4].

In the arcuate nucleus, leptin binds to its receptor (cytokine type 1 receptor) and activates the JAK-STAT (Janus Kinase – Signal Transducer Activator of Transcription) signaling pathway, which functions in both neuronal subpopulations of POMC [42].

Obesity has a direct link with leptin resistance. Evidence suggests that circulating levels of leptin in obese individuals exceed physiological norms several times. Main mechanisms include genetical and environmental factors, defective leptin transport through the blood-brain barrier, and dysfunction of the leptin receptor caused by downregulation and/or alterations. The JAK-STAT pathway disruption at different points or improper feedback mechanism also may cause leptin resistance. Another cause of impaired leptin signaling can be considered inflammation, which is common for many chronic diseases, including obesity [21]. Leptin resistance is tightly associated with insulin resistance, considering common pathways activated in the signaling of both hormones, such as the insulin receptor substrate (IRS) / phosphoinositide-3-kinase (PI3K) pathway. The next step is the activation of Akt or Protein kinase B [48]. Despite similarities, the outcome for insulin and leptin differs. Insulin effects are exerted primarily on the level of insulin-sensitive tissues, hence leptin signaling provides neuroendocrine control and activates neural circuits responsible for maintaining energy balance and appetite suppression. Interestingly, type 1 diabetic patients, if leptin signaling is working properly, are in better conditions than diabetic patients with leptin resistance [29].

Leptin effects are not limited to suppression of food intake: it also has a significant effect on the level of reward circuits [18]. The reward circuits are tightly interconnected with the homeostatic systems of the brain. This interconnection balances the motivation to receive a reward in a hypoenergetic state and reversely lowers the motivation for food intake when an organism has no deficiency in energy [11]. Leptin directly affects mesolimbic dopaminergic system structures, such as the Ventral Tegmental Area (VTA), modulating dopaminergic neurons, which causes suppression of food intake. There is a negative correlation between leptin levels and response to food cues. Simultaneously, leptin affects the hippocampus and amygdala which also show altered functioning, reducing retrieval of memories concerning receiving a food reward and lowering the emotional value of the food reward, respectively [19].

Along with all the mentioned effects, leptin also has a significant role in cell protection. Leptin production is increased in the expansion of adipose tissue, which happens in obesity. Adipose tissue experiences the development of a hypoxic state in adipocytes. Hypoxia induces increased leptin synthesis and causes the development of a mild inflammatory state [23]. Expansion of adipose

tissue leads to the expression of caveolin-1. Simultaneously, leptin suppresses on transcriptional and translational level expression of perilipin, a protein present on the surface of lipid droplets, thus suppressing accumulation of the fat in the adipocytes [35]. The active expansion of adipose tissue leads to the death of the adipocytes, which express chemoattractant, thus recruiting immune cells, such as monocytes to the adipose tissue [23].

Leptin has a modulatory role in inflammation. This unique hormone exerts pro- and anti-inflammatory properties under different circumstances. The anti-inflammatory effect of leptin is exerted predominantly on the adipose tissue level, suppressing the production of pro-inflammatory cytokines, such as tumor necrosis factor–α (TNF-α), interleukin-6 (IL-6), IL-1β, simultaneously promoting the production of anti-inflammatory molecules, such as IL-10 [24]. But in the abnormally high levels of leptin, which is common for obesity, leptin exerts pro-inflammatory properties, causing low-grade inflammation. In such a situation, it activates adipose tissue and immune cell inflammatory pathways, causing the development of systemic inflammation [32].

Depending on the concentration of leptin, it exerts either anti-inflammatory or pro-inflammatory effects on the central nervous system. In physiological levels and healthy body mass index, leptin reduces the release of pro-inflammatory cytokines and promotes the production of anti-inflammatory cytokines from brain macrophages, thus protecting neurons against inflamematory damage. It shows neuroprotective effects, suppressing apoptotic signals and oxidative stress in neurons. Leptin enhances synaptic plasticity contributing to cognition [10]. In abnormally high levels, or in disrupted transport or signaling leptin can stimulate microglial activation with subsequent production and release of pro-inflammatory cytokines, thus contributing to the neuroinflammation. High levels of leptin are associated with potential damage to the blood-brain barrier, which facilitates the entry of diverse pathogens and inflammatory molecules into the brain, contributing to neuroinflammation [5].

Adiponectin is another adipokine secreted solely by the adipose tissue. It is in a negative correlation with the amount of adipose tissue. In the periphery, adiponectin has a key role in enhancing insulin sensitivity in adipose tissue, liver, and skeletal muscles, thus contributing to glucose uptake and maintaining physiological levels of glucose in the blood. It induces lipolysis and oxidation of fatty acids. Lean individuals have higher levels of circulating adiponectin and reversely, obese individuals show reduced levels of this adipokine [8]. Adiponectin has well-expressed anti-inflammatory properties, which have a key role in reducing adipose tissue inflammation and suppressing pro-inflammatory cytokines in adipose tissue. In the adipose tissue it is involved in differentiation and adipogenesis, thus maintaining balance between mature adipocytes and precursor cells. Outside adipose tissue, adiponectin exerts a regulatory effect on blood vessels, showing anti-atherogenic effects and contributing to cardiovascular health [45]. Circulating adiponectin also crosses the blood-brain

barrier, and binds to two types of receptors: AdipoR1 and AdipoR2. The exact effects of adiponectin in the brain are not studied well yet, hence, AdipoR1 shows wide distribution over the brain, and AdipoR2 is expressed only in the hippocampus and hypothalamus. Hence, an expression of AdipoR1 is found in the VTA neurons, suggesting the role of adiponectin in modulating dopaminergic neuron activity [27].

Resistin is a small adipokine, which is primarily associated with insulin resistance. Increased levels of resistin impair insulin sensitivity in peripheral tissues and may lead to type 2 diabetes development [13]. More research is required to understand the exact mechanism of resistin-induced insulin resistance. It has well-expressed pro-inflammatory properties and increases the production of pro-inflammatory cytokines, as well as stimulates the expression of adhesion molecules in endothelial cells. The resistin-induced inflammation is mediated through the binding of resistin to Toll-like receptor 4 (TLR4). Resistin has been reported to be involved in the pathophysiological mechanisms of many inflammation-associated diseases. In adipose tissue, resistin maintains a balance between lipogenesis and lipolysis. Dysregulation of resistin functioning may serve as a cause for the development of obesity and cardiovascular diseases [22]. Resistin effects are not limited to the periphery: it might also affect the central nervous system. Studies with the application of animal models show wide expression of resistin receptors in brain regions involved in energy homeostasis, appetite regulation, and reward-associated areas [49].

Conclusion

The peripheral and central effects of reward-associated adipokines highlight the interplay between metabolic signaling and neural circuits implicated in reward and motivation. These adipokines, primarily secreted by adipose tissue and involved in metabolic regulation, exhibit multifaceted roles in both peripheral tissues and the central nervous system.

Peripherally, adipokines such as adiponectin, visfatin, and chemerin exert significant influence on metabolic homeostasis. Adiponectin, known for its insulin-sensitizing properties, enhances glucose metabolism, promotes fatty acid oxidation, and modulates inflammation, contributing to homeostasis. Visfatin, functioning in NAD^+ biosynthesis, holds implications for cellular resilience and metabolic processes. Chemerin, involved in immune responses and adipogenesis, links metabolic regulation with inflammatory and adipose tissue functions.

Centrally, the exploration of these adipokines in reward circuits is an emerging area of research. While their direct impact on reward-associated neural pathways remains less understood, preliminary evidence suggests potential connections between adipokines and neural processes underlying reward, motivation, and mood regulation. Adiponectin, visfatin, and chemerin

might indirectly influence brain function, impacting behaviors related to reward processing, addiction, and mood disorders. However, further investigation is necessary to understand precise actions and signaling mechanisms within the brain's reward circuits.

The convergence of metabolic signaling pathways with neural mechanisms controlling reward suggests a complex bidirectional communication system between peripheral tissues and the brain. Understanding the crosstalk between adipokines and reward-related neural networks holds promise for unveiling novel therapeutic approaches targeting both metabolic disorders and neuropsychiatric conditions linked to reward dysregulation. Further research elucidating the peripheral and central effects of these adipokines in the context of reward-associated behaviors will illuminate their potential roles in maintaining metabolic health and modulating brain functions related to reward and motivation.

Accepted 28.12.23

Периферические и центральные эффекты адипокинов, ассоциированных с вознаграждением

А.С. Арутюнян

Уровень ожирения значительно вырос за последние несколько десятилетий, вызывая существенные проблемы для системы здравоохранения, такие как нарушение опорно-двигательного аппарата, неприятные ощущения и боль во время движения и выполнения повседневной деятельности, гормональный дисбаланс, инсулинорезистентность, снижение скорости обмена веществ и, наконец, проблемы социального и психологического характера. Этот факт подчеркивает важность исследований, сфокусированных на причинах ожирения. Одной из основных причин ожирения считается нарушение функционирования системы вознаграждения мозга, ответственной за гедонический аспект получения, обработки и формирования ответа на вознаграждение. Жировая ткань является игроком в регулировании голода и сытости, производя и выпуская гормоны, которые транспортируются через гематоэнцефалический барьер и связываются с их рецепторами в гомеостатических и гедонических областях мозга.

Ожирение характеризуется повышенным производством висцеральной и подкожной жировой ткани, что связано с изменением уровней адипокинов, таких как лептин, адипонектин и т.д. Различные адипокины имеют про- или противовоспалительные эффекты. Перепроизводство провоспалительных адипокинов вызывает хроническое воспаление, которое является одной из основных характеристик ожирения.

Целью данного исследования является рассмотрение основных адипокинов, которые вовлечены в процесс обработки вознаграждения на уровне центральной нервной системы.

Պարգևատրման մեջ ներգրավված աղիպոկինների ծայրամասային և կենտրոնական ազդեցությունները

Հ.Ս. Հարությունյան

Ճարպակալումը զգալի աճ է գրանցել վերջին մի քանի տասնամյակների ընթացքում՝ առաջացնելով մի շարք մարտահրավերներ առողջապահական համակարգի համար, ինչպիսիք են հենաշարժիչ համակարգի գործունեության խանգարումը, տհաճ զգացողությունները և ցավը շարժման և առօրյա գործունեության ընթացքում, հորմոնալ խանգարումները, ինսուլինային ռեզիստենտությունը, նյութափոխանակային, ինչպես նաև սոցիալական և հոգեբանական բնույթի խնդիրներ: Այս փաստն ընդգծում է ճարպակալման պատճառների ուսումնասիրության նշանակալիությունը: Ճարպակալման ընդհանուր պատճառներից մեկը համարվում է ուղեղի պարգևատրման ուղիների աշխատանքի խանգարումը, որը պատասխանատու է պարգևատրում ստանալու, մշակելու և դրա նկատմամբ պատասխան ձևավորելու հեդոնիկ ասպեկտների համար: Սովի և հագեցման կարգավորման նշանակալի մասնակից է ճարպային հյուսվածքը: Այն արտադրում և արտազատում է մի շարք հորմոններ (աղիպոկիններ), որոնք տեղափոխվում են արյուն-ուղեղային պատնեշով և կապվում իրենց ընկալիչների հետ ուղեղի հոմեոստատիկ և հեդոնիկ կենտրոններում:

Ճարպակալումը բնութագրվում է ներքին օրգանների և ենթամաշկային ճարպային հյուսվածքների ավելացմամբ, որի արդյունքում դիտվում են մի շարք աղիպոկինների քանակական փոփոխություններ, որոնց թվում են լեպտինը, աղիպոնեկտինը և այլն: Տարբեր աղիպոկիններ ունեն պրո- կամ հակաբորբոքային ազդեցություն: Պրոբորբոքային աղիպոկինների գերարտադրությունն առաջացնում է քրոնիկական բորբոքում, որը ճարպակալման հիմնական բնութագրիչներից է:

Այս աշխատանքի նպատակն է լուսաբանել կենտրոնական նյարդային համակարգի մակարդակում պարգևատրման գործընթացում ներգրավված հիմնական աղիպոկինները:

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