Adipokines and etiopathology of metabolic disorders

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ABSTRACT

انتشار السمنة لفت الانتباه إلى طبيعة الأنسجة الدهنية، إذ تعتبر الأنسجة الدهنية البيضاء غدة صماء تفرز العديد من البروتينات المعروفة باسم أديبوكاينز مثل اللبتين والأديبونكتين والريسيستين والفيسفاتين وعوامل أخرى لها دور في السمنة ومضاعفاتها. ولقد وجد أن مستوى اللبتين وإنتاجه يزداد في حالات السمنة نتيجة لوجود مقاومة لعمل اللبتين ربما تكون ناتجة عن نقص في مستوى انتقاله في المخ أو تثبيط عمله في الغدة تحت السريرية، ويعتبر العمل الأساسي للبتين هو تثبيط الشهية، وتشجيع أكسدة الدهون وتقليل مستوى الجلوكوز في الدم وتقليل الوزن والدهون. أما الأديبونكتين يعتبر نقصه مصاحب لحالات المقاومة للأنسولين، وخلل الدهون في الدم وتصلب الشرايين في الإنسان والفئران وهذا النقص يعتبر مؤشر للإصابة بمرض السكري من النوع الثاني. وبالنسبة للرسيستين في الإنسان فإنه يفرز بقلة من النسيج الدهني وبكثرة من نخاع العظم والرئة، ودوره في تنظيم السكر بالدم لا يزال غامض لقد وجد أنه مصاحب لحالات مقاومة الأنسولين والسمنة في بعض الدراسات. ولقد أثبتت بعض الدراسات أن زيادة مستوى الفيسفاتين في الدم والأنسجة الدهنية في حالات السمنة لكي يحافظ على الحساسية للأنسولين، وهو يشابه الأنسولين في عمله حيث أنه يزيد استهلاك الجلوكوز في الأنسجة الدهنية ويثبط إنتاج الجلوكوز من الكبد، كما يساعد على تنشيط مستقبل الأنسولين. وما زالت الدراسات مستمرة لتضيء الضوء على دور الأديبوكاينز لدى الأمراض الأيضية.

White adipose tissue is an endocrine organ producing numerous proteins known as adipokines, which include leptin, adiponectin, resistin, visfatin, and other factors, which are involved in most metabolic disorders. In obesity, plasma leptin concentrations are high due to leptin resistance that may result from the attenuation of leptin signaling in the hypothalamus. Leptin acts to inhibit appetite, stimulate thermogenesis, enhance fatty acid oxidation, decrease glucose, and reduce body weight, and fat. A reduced adiponectin level has been associated with insulin resistance, dyslipidemia, and atherosclerosis, and its low level is a predictor of later development of type 2 diabetes. Resistin expression is low in adipose tissue and high in bone marrow and lungs, its role in glucose homeostasis remains controversial, it has been associated with insulin resistance and obesity. Visfatin is a secretory protein highly enriched in visceral adipocytes, liver, muscle, and lymphocytes. An increase of visfatin levels in obesity was related to preservation of insulin sensitivity, it enhances glucose uptake by adipocytes and inhibits hepatocyte glucose release, it induces tyrosine phosphorylation, and interacts with insulin receptors. Many studies are still being conducted to highlight the role of adipokines in metabolic disorders.

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Obesity is closely linked to a roster of chronic metabolic abnormalities including insulin resistance, type 2 diabetes mellitus, hypertension, hyperlipidemia, atherosclerosis, and even cancer. Obesity has reached an epidemic proportion and has focused attention on the biology of adipose tissue. White adipose tissue (WAT) for a long time was regarded as a site of energy store in the form of triglycerides.[1] This energy is accumulated during periods of excess food intake and mobilized when calorie intake is inadequate. Adipocytes provide a large energy storage capacity mainly in the form of triglycerides.[2] During feeding, the levels of insulin, glucose, and nutrients increase to stimulate energy storage in the liver and adipocytes. Conversely, fasting enhances glycogenolysis, and gluconeogenesis via activation the sympathetic nervous system, increasing the levels of glucagon, epinephrine, and glucocorticoids leading to maintenance of the glucose supply to the brain and vital organs.[2] Prolonged fasting also stimulates lipolysis, generating fatty acids to be used by muscle,

liver, and peripheral organs, and providing ketones for the brain.[2] The increase in WAT mass in obesity is associated with profound histological and biochemical changes characteristic of inflammation.[3,4] Studies in obese humans and rodents have shown an increase in activated macrophages that form giant cells, which produce tumor necrosis factor (TNF)-α, interleukin-6 (IL-6), various cytokines, and C-reactive protein.[3,4] The levels of intracellular cell-adhesion molecule-1 and platelet/endothelial cell adhesion molecule-1 increase in adipose endothelial cells, inducing the migration and adhesion of monocytes.[2,5] The aim of this article is to highlight the main role of various adipokines in the pathophysiology of some metabolic disorders such as obesity, inflammation, diabetes, and atherosclerosis. And finally, although diet and exercise remain the gold standards of obesity treatment, novel interventions have to be discovered that would give promising results in at least controlling if not preventing both the exponential growth of the obese population and the morbid complications of being chronically obese.

Literature review. A number of studies[1,6] indicate that WAT is an endocrine organ producing numerous proteins known as adipokines, such as leptin, adiponectin, acylation stimulating protein, and other factors, which are important and involved in maintaining energy homeostasis.[7] Adipokines are also involved in obesity associated complications, such as insulin resistance, endothelial dysfunction, arterial hypertension, and atherosclerosis.[6]

Leptin. Leptin comes from the Greek word leptos meaning thin and it is termed the obese (ob) gene. Cloning of the ob gene was demonstrated.[8] The ob gene is a 16kD peptide hormone, synthesized by fat cells mainly by adipocytes, although a number of tissues including the gastric fundic epithelium, intestine, placenta, skeletal muscle, mammary epithelium, and brain produced leptin in low levels.[9] Leptin is secreted into the blood stream and circulates in free or inactive bound form, the concentration of leptin is higher in obese than lean individuals.[10] The ob/ob mice are obese because they fail to produce leptin, whereas $Lepr^{db/db}$ mice are resistant to leptin because of a mutation in one of the leptin receptors.[11] Leptin replacement in the ob/ob mice causes a marked reduction in food intake and a reduction in the body weight.[12-14] The leptin structure is similar to members of the long-chain helical cytokine family.[15,16] A disulfide bond between cysteine 96 and cysteine 146 are important for structure folding and receptor binding.[16] The biological activity of leptin is localized in the carboxy-terminal of the protein, in the domains between residues 106-167.[17,18] The peak in serum leptin level is highest between midnight and early morning and lowest around noon to mid-afternoon.[19] This circadian rhythmicity of leptin is similar to the circadian rhythmicity of thyrotropin, prolactin, free fatty acid, and melatonin,[20] but inversely related to that of adrenocorticotropic hormone (ACTH) and cortisol.[21] A higher leptin level in women is explained partly by increased production in subcutaneous adipose tissue and stimulation by estrogens. Chronic glucocorticoid exposure, TNF-α, and IL-6 also increase leptin. On the other hand, leptin is suppressed by androgens in males, and by adrenergic stimulation.[10] Circulating leptin levels exhibit pulsatile release with pulse duration of approximately 30 minutes, which is inversely related to rapid fluctuations in plasma cortisol and adrenocorticotropic hormone (ACTH).[21,22] Leptin pulsatility is synchronous to the pulsatility of circulating luteinizing hormone (LH) and oestradiol in normal women.[23] Leptin is one of the well documented hormones of the adipose tissue in terms of physiology and pathology. It was first identified as the product of the ob gene in leptin deficient obese (ob/ob) mice and was originally described as a circulating hormone involved in feeding behavior and energy homeostasis.[24] Obesity is associated with high plasma leptin concentration and with leptin production. This rise in endogenous leptin or with exogenous leptin treatment was unable to prevent weight gain in obese humans and rodents. This apparent "leptin resistance" may result from a decrease in brain transport or attenuation of leptin signaling in the hypothalamus.[9,25] Also, leptin resistance has been attributed to induction of the suppressor of cytokine signaling 3 (SOCS3) and protein tyrosine phosphatase 1B, which normally inhibits leptin signal transduction.[7,26-29] The leptin receptor (LR) belongs to the cytokine receptor class I family, containing extracellular ligand-binding, transmembrane, and cytoplasmic signaling domains.[25,30] There are various leptin receptor isoforms LRa, LRe, and LRb, however, leptin's effects on energy homeostasis are thought to involve the long receptor LRb, especially in the brain.[7,9] Leptin transports across the blood-brain barrier (BBB) through a saturable mechanism, but the specific mechanism of the "leptin transporter" is still unknown.[31,32] Leptin controls specific neurons within the hypothalamus, brain stem, and other regions of the CNS.[9] Leptin uptake is high in the hypothalamus, which is consistent with the role of the hypothalamus in energy homeostasis. Fatty acids and amino acids have also been implicated in the disruption of leptin signaling in the hypothalamus.[7,34,35] The biological role of leptin uptake in the hippocampus, olfactory tubercle, thalamus, and cerebral cortex is still unclear.[33] High LRb expression is present in the arcuate, dorsomedial, entromedial, and ventral premamillary hypothalamic

nuclei, moderate LRb expression is present in the periventricular region and posterior hypothalamic nucleus, and low LRb levels are expressed in the paraventricular nucleus (PVN) and lateral hypothalamic area (LHA).[9,36] Leptin crosses the blood-brain-barrier, and acts directly on neurons in the arcuate nucleus that express neuropeptide Y (NPY), agouti-related peptide (AGRP), pro-opiomelanocortin (POMC), and cocaine- and amphetamine-regulated transcript.[4] An increase in leptin directly suppresses the orexigenic peptides NPY and AGRP in the arcuate nucleus and indirectly inhibits the melanocortin-concentrating hormone (MCH) and orexins, which are expressed in the LHA.[7] Leptin increases the level of anorectic peptides, α-melanocyte stimulating hormone (α-MSH) derived from POMC and cocaine and amphetamine-regulated transcript, produced by neurons in the lateral arcuate nucleus. These project to the PVN to increase corticotrophin-releasing hormone, thyrotropin releasing hormone, and oxytocin. The net action of leptin is to inhibit appetite, stimulate thermogenesis, enhance fatty acid oxidation, decrease glucose, and reduce body weight and fat.[7,37-39] Leptin acting through LRb has been shown to regulate insulin receptor substrate 1 and 2, mitogen-activated protein kinase, extracellular signal-regulated kinase, AKt and PI3 kinase, raising the possibility of cross-talk between leptin and insulin.[7,40] The leptin signal is transmitted by the Janus Kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. Binding of leptin to LRb results in autophosphorylation of JAK1 and 2, and activation of STAT3.[30] The leptin signal is terminated through induction of (SOCS)-3 that inhibits JAK-STAT signaling.[7,9] Ablation of SOCS3 neurons enhances leptin action, resulting in STAT3 activation, an increase in hypothalamic POMC expression, and reduction in food intake and weight.[7,27] Protein-tyrosine phosphatase-1B, which is well known to terminate insulin action, also inhibits leptin signaling through inactivation of JAK2. The protein tyrosine phosphatase-1B deficient mice exhibits greater leptin sensitivity, increased hypothalamic STAT3 phosphorylation, and resistance to obesity.[7,28] Adenosine monophosphate (AMP)-activated protein kinase is another leptin target.[41] Adenosine monophosphate kinase (AMPK) is phosphorylated and activated in response to energy deficit during fasting or cellular stress, leading to stimulation of fatty acid oxidation. Hypothalamic AMPK phosphorylation and activity are increased by fasting and decreased by leptin, insulin, and various anorectics. Leptin inhibits the phosphorylation and activation of AMPK in the hypothalamus, leading to appetite suppression.[7,42] Leptin improves insulin sensitivity through activation of AMPK, which controls cellular concentrations of malonyl-CoA. In the presence of leptin, AMPK is activated and acetyl-CoA carboxylase enzyme is inhibited, and the conversion of acetyl-CoA to malonyl-CoA is inhibited, therefore, malonyl-CoA level falls, fatty acid oxidation increases, and the lipid content decreases.[43,44] On appetite, leptin depolarizes hypothalamic POMC neurons and decreases the inhibitory tone of γ-amino butyric acid.[44] Conversely, leptin hyperpolarizes and inactivates NPY neurons in the arcuate nucleus.[45,46] The fall in leptin during fasting increases the action potential frequency in NPY neurons, and this correlates with hyperphagia.[46,47] On the other hand, leptin hyperpolarizes glucose-responsive neurons in the hypothalamus, an effect that has been linked to appetite suppression and weight loss.[7,48] Leptin plays a dual role in energy homeostasis. During fasting, the fall in leptin signals to the brain, leading to hyperphagia, reduced energy expenditure, and suppression of thyroid, reproduction and growth hormones, and the immune system.[49,50] Furthermore, fasting-induced hypoleptinemia increases NPY and AGRP and reduce POMC neurons in the hypothalamus.[10,51] In agreement, previous studies[10,52] denote that leptin deficiency induces hyperphagia and changes in neuroendocrine and immune function during fasting. Leptin seems to control hepatic glucose production through a central melanocortin-dependent pathway that stimulates gluconeogenesis and a melanocortin-independent pathway that inhibits glucose production and glycogenolysis. Administration of leptin by intravenous and intra-cerebroventricular infusion enhances peripheral insulin action.[53-56] Acute leptin infusion in the cerebral ventricle stimulates gluconeogenesis with a compensatory decrease in glycogenolysis, so it does not affect glucose production.[57] Gutierrez-Juarez et al[58] found that blockade of the central melanocortin pathway prevents the effects of leptin on glucose production. These previous data establish the crucial role of leptin in the CNS regulation of glucose metabolism that may relate to the pathogenesis of insulin resistance and type 2 diabetes associated with obesity.[7,59] The administration of recombinant leptin is performed intravenously, intra-muscularly, intraperitoneal, and through other parenteral routes to treat obesity and diabetes. Leptin injections evoke weight loss by causing a reduction in food consumption and an increase in energy expenditure.[60] Oosman et al[60] recently introduced the concept of transplanting gut-derived cells that are engineered to produce leptin, under the regulation of an inducing agent, mifepristone among obese, diabetic ob/ob mice and to mice fed on a high-fat diet. They found out that transplantation of these cells offers a therapeutic effect in leptin-deficient mice alone.

Adiponectin. Adiponectin is a 30-kDa collagen-like protein, clinically noted to be anti-atherogenic and anti-diabetic at elevated levels.[61] It is an adipocyte-secreted protein of 247 amino acids, produced exclusively by adipocytes. Adiponectin contains an N-terminal signal sequence, a variable domain, a collagen like (tail) domain, and C-terminal globular (head) domain.[7,62] The structure of the globular domain resembles TNF-α.[63] In the circulation, adiponectin exists in 2 forms, a low molecular weight (LMW) oligomer, and as high molecular weight (HMW).[63,64] The potency of adiponectin has been linked to the HMW complex.[7,65] The adiponectin protein can undergo proteolytic cleavage leading to the formation of the globular form of adiponectin containing only the globular head domain.[66] The globular form of adiponectin stimulates β-oxidation of fatty acids in skeletal muscle, whereas the full-length adiponectin decreases hepatic glucose output.[10,66-68] Adiponectin is abundant in the circulation with remarkably high concentrations in human blood (approximately 10 μg/ml), accounting for 0.01% of total serum protein.[69] Males have significantly lower plasma adiponectin than females.[70,71] This gender difference between women and men is due to the inhibitory effect of androgens on adiponectin.[72] Reduced adiponectin levels have been associated with insulin resistance, dyslipidemia, and atherosclerosis in humans and rodents,[63] in patients with cardiovascular disease,[73] and diabetes.[74] Epidemiological studies showed that low levels of adiponectin are a predictor of the later development of type 2 diabetes,[75,76] and myocardial infarction.[77,78] The AdipoR1 and AdipoR2 are the receptors of adiponectin, with AdipoR1 being expressed in muscle tissues as a high-affinity receptor for globular adiponectin and low affinity for full-length adiponectin, whereas AdipoR2 is abundantly found in the liver and serves as an intermediate-affinity receptor for both forms of adiponectin. The function of adiponectin in various glycemic and lipid processes can be explained by activation of AMPK and stimulation of peroxisome proliferator-activated receptor (PPAR) alpha, which leads to increased glucose uptake and oxidation of fatty acids in skeletal muscle and decreased hepatic glucose output.[79] Although studies have failed to demonstrate a blood-brain transport of adiponectin, both AdipoR1 and AdipoR2 are distributed widely in the brain.[80] Injection of adiponectin into the fourth ventricle depolarized AdipoR1 and AdipoR2-positive neurons in the area of postrema, suggesting a potential mechanism for its central adiponectin action.[7,81] The Adipo R1 was shown to interact with the insulin receptor, thereby enhancing insulin signal transduction, and by this mechanism adiponectin could ameliorate insulin resistance. Adiponectin treatment enhances insulin sensitivity, primarily by suppressing glucose production.[10,68,82,83] Targeted disruption of AdipoR1 prevented adiponectin-induced AMPK activation, whereas disruption of AdipoR2 decreased PPAR-α activity.[84] Disruption of both Adipor1 and AdipoR2 abolished adiponectin binding and induced steatosis, inflammation, oxidative stress, insulin resistance, and glucose intolerance.[10,84] In skeletal muscle, adiponectin increases expression of molecules involved in fatty-acid transport such as CD36, in combustion of fatty acids such as acyl-coenzyme A oxidase, and in energy dissipation such as uncoupling protein 2, leading to decreased triglyceride contents.[85] On the vascular system, adiponectin has implicated activation of AMPK and inhibition of nuclear factor κB (NF-κB) and vascular adhesion molecules. Adiponectin also exerts a protective action in myocardial remodeling in response to acute ischemia-reperfusion.[10,86] Adiponectin deficient mice had increase myocardial apoptosis and infarct size than wild-type. Importantly, adiponectin treatment diminished infarct size, apoptosis and TNF-α production in both knockout and wild-type mice. These actions appear to be mediated through activation of AMPK, and induction of cyclooxygenase-2-dependent synthesis of prostaglandin E2.[10,86] Plasma adiponectin levels are found to be lower in obese subjects than in lean subjects, and strong negative correlations between plasma adiponectin levels and body mass index have been shown both in humans and in animals.[70,71,87] In accordance with these findings, the adiponectin mRNA levels are also lower in adipose tissue from obese as compared with lean subjects.[88,89] In addition, adiponectin gene expression and protein levels are higher in subcutaneous than in intra-abdominal adipose tissue.[89,90] Adiponectin is markedly reduced in obesity and rises with prolonged fasting and severe weight reduction.[10,82,83] Peripheral adiponectin treatment decreases body weight, specifically fat, by increasing the stimulating oxidation of fatty acids.[7,91] Adiponectin potentiated the central effects of leptin to increase thermogenesis and fatty acid oxidation and reduce glucose and lipids in Lep $^{ob/ob}$ mice.[92] In contrast, dominant agouti (Ay/a) mice failed to respond to both leptin and adiponectin, implying a common involvement of melanocortin receptors.[92] Recent reports showed that in prostate cancer, adiponectin was observed to be higher in locally advanced relative to organ-confined prostate cancer, and may thus serve as an auxiliary marker providing further improvement to PSA (prostate-specific antigen) for discrimination between different stages of prostatic cancer.[93]

Resistin. Resistin belongs to a family of cysteine-rich C-terminal domain proteins called resistin-like molecules (RELMs). There are 4 members in the mouse RELMs family: resistin, RELMα, RELMβ,

and RELMγ. Only 2 counterparts were found in humans, resistin and RELMβ.[94] The mouse resistin gene is localized to chromosome 8 and the human resistin gene to chromosome 19.[94] Mouse resistin is almost exclusively expressed in white adipose tissue with high levels, whereas human resistin is expressed with low levels in the adipose tissue and expressed with high levels in bone marrow followed by the lung.[94] Additionally, human resistin has been detected in placental tissue,[95] and pancreatic islet cells,[96] although resistin gene expression is largely confined to macrophages.[94,97] Studies in rodents suggest that resistin inhibits the phosphorylation and activation of AMPK, and induces SOCS3 production.[98-100] Unlike rodents, where resistin is produced exclusively by adipocytes, human resistin is secreted by mononuclear cells and activated by macrophages.[10,97] The role of resistin in glucose homeostasis in humans remains controversial.[101] Resistin has been associated with insulin resistance and obesity in some studies, but others have failed to establish such a relationship.[102-106] A connection between resistin, inflammation, and atherogenesis has been reported.[10,107-109] The role of resistin in the development of inflammation and its relationship with adipokines remains unknown. Previous works showed a correlation between resistin and inflammatory markers.[109-112] Kaser et al[112] demonstrated that in human mononuclear cells, resistin mRNA expression is regulated by pro-inflammatory cytokines such as IL1, IL6, and TNFα. This association signifies the relationship between resistin and inflammation.[112] Other investigators have demonstrated a strong correlation between resistin and plasma levels of sTNFR2 in diabetic patients.[113,114] Human studies of the association between resistin and inflammation has shown increased serum levels of resistin in acute inflammatory processes.[115,116] These results support the suggestion that resistin may play an inflammatory rather than a metabolic function in humans.[117,118] In humans, hyper-resistinemia is indirectly regulated by an inflammatory process accompanying the obesity. Therefore, resistin seems to be a possible mediator of insulin resistance in humans with acute inflammation.[114] Resistin antagonizes insulin action both *in vivo* and *in vitro*. Resistin concentrations were higher in obese and diabetic mice. Administration of resistin increased plasma glucose levels and stimulated endogenous glucose production in rodents.[117,119] The deficiency of resistin decreases hepatic gluconeogenesis and glucose levels.[117,120]

Visfatin. Visfatin is a secretory protein highly enriched in rodent and human visceral adipocytes; and is also expressed by liver, muscle, bone marrow, and lymphocytes, where it was first identified as pre-B-cell colony stimulating factor.[121] Initial study described an increase in adipose and circulating visfatin in obesity, and this was related to preservation of insulin sensitivity.[121] Visfatin appeared to exert an insulin-mimetic effect in adipocytes, and hepatocytes following systemic administration in the mice.[10,121] Visfatin shows similarity to insulin in vitro, it enhances glucose uptake by myocytes and adipocytes and inhibited hepatocyte glucose release.[121] In addition, visfatin amplifies adipocyte differentiation. Its insulin-like effects are also observed in the insulin-transduction pathway, as this hormone induces tyrosine phosphorylation of insulin receptors IRS-1 and 2, and activation of phosphatidyl inositol-3 kinase, protein kinase B, and MAP kinase. Also, visfatin and insulin have the same affinity for the insulin receptor, with visfatin physically interacting with the receptor, but at a different site. Despite this similarity between visfatin and insulin, there are also important differences.[121] Visfatin levels do not significantly change in fed or fasting states. Plasma levels of visfatin are lower, 10% of insulin levels in a fasting state and 3% in a fed state. These differences in plasma concentrations could account for the mild effect of visfatin in glycemia. Although it is too early to consider visfatin in the development of hypoglycemic drugs, recent research has shown that serum visfatin increases with progressive beta-cell deterioration in type 2 diabetic patients.[122] Intravenous infusion of visfatin in normal rats leads to an acute fall in glucose, independent of insulin secretion.[121] Visfatin-deficient animals (–/–) are not compatible with life. Heterozygous animals (visfatin +/–) have two-thirds lower visfatin blood levels than wild-type mice. On the other hand, growth rate, total body weight, food intake, and brown fat levels in muscle and heart are no different from wild-type mice.[121] Indeed, in adipose tissue, visfatin is preferentially expressed by macrophages rather than mature adipocytes.[123] Visfatin was originally identified as a pre-B-cell colony-enhancing factor (PBEF) that acts as growth factor for early-state B cells, it is also expressed in neutrophils from critically ill patients with sepsis in whom rates of apoptosis are profoundly delayed.[124,125] So visfatin acts as recombinant PBEF, which exerts anti-apoptotic effects through inhibition of caspases-3 and -8. It can be considered as an inflammatory cytokine that plays an essential role in delayed neutrophil apoptosis in clinical and experimental sepsis.[125,126] It could also represent a useful biomarker in acute lung injury,[127] and is also highly expressed in carotid plaques from symptomatic individuals within lipid-rich macrophages.[128] There is also a relationship between visfatin and unstable lesions in patients with coronary heart disease, and it can increase matrix metalloproteinase-9 activity in monocytes, and TNF-α and IL-8 in peripheral blood mononuclear cells.[128]

In conclusion, this review highlights the notion that

the adipose tissue has complex interactions with the brain and peripheral organs via adipokines. Leptin and various adipokines have paracrine autocrine actions, which serve to modulate adipogenesis, glucose, and lipid metabolism, immune and neuroendocrine functions. Leptin biology in normal individuals and its role in obesity related disorders and how it reach its targets, its receptors, its effects on feeding, lipids, and hormonal regulation, and whether leptin resistance play a role in obesity are clarified in this article. It is leptin resistance and not leptin deficiency per se, which is regarded as a pathogenic mechanism in human obesity. Among its vital functions, leptin acts via hypothalamic receptors to inhibit feeding and increase thermogenesis, resulting in a decreased body weight. Evidence also suggests that leptin has an inhibitory role on insulin secretion. The above-mentioned findings are just a fraction of how leptin influences body metabolism, making it a very promising target for therapeutic interventions for a multiple of metabolic diseases. This article also provides a framework for understanding how adiponectin helps to reduce body weight and to resist obesity, also it could be used as a marker for cancer prostate. The article highlights that in humans, resistin is indirectly regulated by the inflammatory process accompanying obesity, it antagonizes insulin action both *in vivo* and *in vitro*. Therefore, resistin seems to be a possible mediator of insulin resistance in humans with acute inflammation. Also, the article illustrates that visfatin shows similarity to insulin and it amplifies adipocyte differentiation. Serum visfatin increases with progressive beta-cell deterioration in type 2 diabetic patients, it has a pre-B-cell colony-enhancing factor (PBEF) that acts as a growth factor for early-state B cells, and exerts anti-apoptotic effects through inhibition of caspases-3 and -8, it is an inflammatory cytokine that plays an essential role in delayed neutrophil apoptosis in clinical sepsis. It could also represent a useful biomarker in acute lung injury, and there is also a relationship between visfatin and unstable lesions in patients with coronary heart disease. Understanding the signaling pathways of adipokines and their targets in the brain and peripheral organs will benefit the treatment of obesity and associated metabolic diseases. Collectively, the results of studies cited herein delineate the basis of adipokines physiology and pathophysiology of obesity related diseases.

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Related topics

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