Peripheral Actions of Leptin and Its Involvement in Disease
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The discovery of leptin is broadening our understanding of the mechanisms underlying neuroendocrine function. To date, most investigations have focused on the effects of leptin on food intake control and body weight homeostasis with attention primarily focused on the central effects of leptin. However, the almost ubiquitous distribution of leptin receptors in peripheral tissues provides a fertile area for investigation and a more dynamic view of leptin is starting to unfold. Thus, leptin has generated enormous interest in the interaction as well as integration between brain targets and peripheral signals. The scientific evidence supporting the direct peripheral effects of leptin on angiogenesis, wound healing, lipolysis, blood pressure homeostasis, and satiety control is reviewed.

Key Words: leptin, neuroendocrine function, brain targets and peripheral signals, angiogenesis, wound healing, lipolysis, blood pressure, homeostasis, satiety control

Introduction

The name of Galileo Galilei is inextricably linked with the advent, early in the seventeenth century, of a marked change in the balance between speculative philosophy, mathematics, and experimental evidence in the study of natural phenomena. The same historic period witnessed Kepler’s mathemetic transformation of planetary theory and Harvey’s experimental attack on physiologic dogma. Historians are divided in their assessment of this widespread scientific revolution with respect to its elements of continuity and innovation, both as to method and as to content. The life and works of Galileo are of central importance to the understanding of this revolution because his personal conflict with religious authority dramatized the extent and profundity of the changing approach to nature.

Before Copernicus and Galileo, the geocentric model placed the earth at the center of the universe and all celestial bodies, including the sun, were thought to revolve around it. The heliocentric model proposed by these two astronomers, on the contrary, identified the sun as the center of the universe, asserting that the earth and all other planets travel around the sun. This changed forever the understanding of the cosmos and a close parallelism can be drawn to the present knowledge of leptin. At the beginning, in what we can call the “geocentric view” of leptin, the brain was considered the center of all leptin effects (Figure 1). The initial concept was that leptin, an adipocyte-derived peptidic hormone, informs the brain about the abundance of body fat, thereby acting as a sensing hormone or lipostat in a negative feedback system from adipose tissue to the hypothalamus. The knowledge of leptin, however, has evolved considerably during the last five years to a “heliocentric view” in which leptin is being placed at the center and the different organs are targets for this hormone. The initial, rather simplistic, notion that leptin participates only in food intake and body weight has developed considerably. For the sake of simplicity, Figure 2 only includes a few organs. However, as many orbits as tissues are present in the body can be added to the schematic representation because all organs are targets for leptin and therefore “rotate” around this hormone. Obviously, in this model the peripheral effects of leptin are considered equally relevant to the actions exerted at the hypothalamic level.

Pleiotropy of Leptin

The “heliocentric view” of leptin is further supported by the universal distribution of functional leptin receptors, reflecting the multiplicity of biologic effects in extra-neural tissues. Leptin was discovered on the basis of a very specific biologic action, namely body weight and appetite regulation. Originally isolated in relation to a particular biologic action, many cytokines have subsequently been shown to be capable of stimulating a variety of biologic responses in a wide spectrum of cell types. Thus, leptin shares with other cytokines an ex-
treme functional pleiotropy and has been shown to participate in quite diverse physiologic functions such as reproduction, hematopoiesis, angiogenesis, immunity, blood pressure control, and bone formation.4–7

**Hematopoiesis and Macrophage Function**

Many cytokines have been shown to exert their biologic effects by binding to members of the hemopoietin receptor family.8 In this context, mRNAs encoding long and short forms of the leptin receptor are expressed in a range of human and murine hemopoietic organs.9,10 The functional form of the receptor is capable of signaling for cell survival, proliferation, and differentiation into macrophages.10 Furthermore, leptin appears to be able to enhance the production of cytokines in macrophages and to increase the attachment and subsequent receptor-mediated process of phagocytosis. This activity may be mediated by an up-regulation of macrophage receptors or by increased phagocytic activity. Interestingly, a role for leukocyte adhesion receptors in maintenance of normal body weight and adiposity has been described.11

**Angiogenesis**

In a serendipitous discovery it was observed that endothelial cells express the long form of the leptin receptor and that it is functionally competent.12 The researchers engineered cultured cells to produce the functional leptin receptor and were using antibodies to confirm that the cells actually contained the long form of the receptor. Endothelial cells were chosen as a negative control because investigators were sure that these cells would not express the leptin receptor. Surprisingly, endothelial cells scored positive for functional leptin receptors, indicating that they are targets for the adipocyte-derived hormone. Leptin has been shown to cause cultured endothelial cells to aggregate, form tubes, and display a reticular array reminiscent of tissue vasculature, and therefore must be included in the list of angiogenic
The angiogenic effects, tested both in vitro and in vivo, indicate that leptin—acting through its endothelial receptor—generates a growth signal that contributes to the promotion of angiogenic processes.

The angiogenic effect of leptin suggests several intriguing possibilities. One is that leptin contributes to the formation of the new blood vessels needed when fat mass increases in volume, thus driving the blood vessels to match the amount of fat. The hormone produced by adipocytes is not only secreted into the bloodstream, but also may act locally upon endothelial cells in a paracrine fashion, assuring an appropriate balance between blood supply and fat depot size. It does not appear to be essential for this function, however, because the enormous fat depots in mutant mice that completely lack leptin manage to recruit an adequate blood supply.

Cell growth, cell migration, and angiogenesis are normal biologic processes hijacked by tumor cells to promote tumor proliferation and invasion. As an angiogenic factor, leptin may be deployed by some cancers to recruit blood vessels. Both primary tumor growth and the formation of metastasis depend on the establishment of new blood vessels. It is interesting to note that rat insulinoma–derived pancreatic beta cells express a functional leptin receptor that mediates a proliferative response.14 Analogously, leptin receptors have been shown to be expressed in human colon cancer cell lines as well as in human colonic tissue.15 In addition, stimulation of colonic epithelial cells with leptin has been reported to increase proliferation both in vitro and in vivo. In this sense, it may be interesting to further explore whether tumor cells are able to produce leptin.

The leptin-angiogenesis connection becomes extraordinarily interesting in relation to the reproductive system. The female reproductive organs exhibit marked periodic growth and regression, including the development and repair of the endometrium during the menstrual cycle. As a matter of fact, the reproductive organs are some of the few adult tissues in which angiogenesis occurs as a normal physiologic process. Ovarian follicles are known to contain and produce angiogenic factors. The expression of vascular endothelial growth factor is known to be greatest during the early luteal phase, coincident with luteal vasularization. In humans serum leptin concentrations have been shown to be higher in the luteal than in the follicular phase.16,17 The relationship between body mass index and circulating leptin has been observed to vary during the course of spontaneous cycles, the best correlation occurring during the luteal phase when progesterone and leptin concentrations are highest.16

Throughout pregnancy, the uterus undergoes rapid as well as progressive, morphologic, and functional modification. During the preimplantation stage of pregnancy, the endometrium provides an environment that sustains embryonic development, and then participates in the nidation process. The endometrium also contributes the maternal component of the fetomaternal placenta. Thus, the angiogenic effect of leptin may help the follicles generate the many new blood vessels they produce as they mature and help the young embryo itself induce the mesh of blood vessels in the placenta.

Epithelialization and Wound Healing

Systematically as well as topically administered leptin has been reported to improve re-epithelialization of wounds in ob/ob mice.19 Leptin completely reversed the atrophied morphology of the migrating epithelial tongue observed at the wound margins of leptin-deficient animals into a well organized hyperproliferative epithelium. Moreover, topically supplemented leptin accelerated normal wound-healing conditions in wild-type mice. Proliferating keratinocytes located at the wound margins specifically expressed the functional leptin receptor subtype during skin repair. In addition, leptin has been shown to mediate in vitro a mitogenic stimulus to human keratinocytes.18

Vascularization and inflammation play an important role in tissue healing after injury. In this sense, the activation of the immune system by leptin together with the angiogenic and wound healing effects of the hormone may prove to be of extraordinary physiologic relevance. Leptin may participate in the development of an inflammatory reaction in infarcted tissue and accelerate tissue repair. The involvement of leptin in the signaling cascade following myocardial infarction is feasible both from a molecular and functional point of view.19 Interestingly, a worse clinical outcome after acute myocardial infarction is observed in obesity,20 in which a state of leptin-resistance has been proposed. The study of the potential participation of leptin may provide valuable information concerning cooperation among different signaling systems and may further the understanding of how the induction of cytokines operates in a cascade fashion.

Bone Formation

The expression of high levels of leptin and leptin receptors in fetal bone and cartilage implies a role for leptin in skeletal development. Recently, leptin has been identified as a potent inhibitor of bone formation acting through the central nervous system.7 Despite suffering from hypogonadism and hypercortisolism, known inducers of increased osteoclast number and bone resorption activity, leptin-deficient and leptin receptor–deficient mice exhibit a high bone mass phenotype. Interestingly, this phenotype is not secondary to obesity, but is directly related to the lack of leptin signaling. Intracerebroventricular infusion of leptin to ob/ob and wild-type mice is followed by a significant bone mass reduction.7 Al-
though this has been reported to be a centrally mediated effect, it is not reckless to think that leptin has a direct effect on bone remodeling operating as a growth factor not only on osteoclasts but also on osteoblasts.

**Lipolytic Activity**

The existence of functional leptin receptors in white adipose tissue pointed to the possibility of leptin’s participation in regulating lipolysis. Previous studies have shown an autocrine-paracrine lipolytic effect of leptin on white adipose tissue both in vitro and in vivo.21–23 Moreover, a novel form of lipolysis in which the leptin-induced glycerol release is not accompanied by a rise in plasma free fatty acids has been demonstrated.24

Adenoviral transfer of the leptin gene into rats has been shown to dramatically reduce tissue triglyceride stores compared with pair-fed controls, providing evidence of the relevance of leptin in lipid metabolism beyond its appetite-reducing properties.25,26 Furthermore, the lipopenic action of hyperleptinemia on adipocytes is reportedly not mediated by neurotransmitted signals from the central nervous system.27 In addition, leptin has been shown to repress acetyl-CoA carboxylase gene expression, fatty acid synthesis, and lipid synthesis, biochemical reactions that contribute to lipid accumulation without the participation of centrally mediated pathways.24,28 Thus, leptin is involved in the direct regulation of adipose tissue metabolism by both inhibiting lipogenesis and stimulating lipolysis. However, the mechanisms of leptin-induced lipolysis still remain to be completely elucidated.

Until recently, the adipocyte has been considered only a passive tissue for the storage of excess energy in the form of fat.29 There is now compelling evidence, however, that adipocytes act as endocrine secretory cells.29–31 Investigators have shown that several hormones, growth factors, cytokines, and their respective soluble receptors are actually expressed in white adipose tissue with a wide range of signals emanating from adipocytes.32 Among others, nitric oxide synthase (NOS) has been reportedly expressed in rat white adipose tissue, indicating that adipocytes are a potential source of nitric oxide (NO) production.33 Recently, evidence for involvement of NO in both rat and human lipolysis has been published.34,35 Interestingly, leptin immunolabeling of white adipocytes exhibits an absolutely superimposable staining pattern to that of inducible NOS.32

The potential role of NO in the leptin-induced effects on lipolysis was investigated taking into consideration the morphologic and physiologic resemblance between NO and leptin. Leptin administration significantly increased serum NO concentrations in a dose-dependent manner.36 Simultaneously, a statistically significant (P < 0.0001) dose-dependent increase in the basal lipolytic rate was observed 1 hour after exogenous leptin administration. Simple linear regression analysis showed that the lipolytic rate measured in white adipose tissue was significantly correlated (P = 0.0025; r = 0.517) with serum NO concentrations (with 27% of the variability taking place in lipolysis depending on the changes in NO concentrations) (Figure 3). Leptin administration significantly increased the lipolytic rate in all experimental groups (Figure 4). Under NO synthesis inhibition by Nω-nitro-1-arginine methyl ester (l-NAME) pretreatment, the leptin-induced stimulation of lipolysis was significantly reduced (P < 0.05) compared with leptin-treated control animals. On the contrary, the effect

![Figure 3](image) Simple linear regression analysis between lipolytic activity measured in white adipose tissue and serum nitrite-nitrate concentrations (r = 0.517; P = 0.0025). The solid line depicts the regression function (y = 8.37 + 10.77x). The dotted lines depict the 95% confidence interval.

![Figure 4](image) Lipolytic activity of white adipocytes obtained from Wistar rats belonging to either the control (saline) or the leptin-treated group. Experimental animals had been previously injected with either vehicle (0.9% NaCl), nitric oxide synthase inhibition (l-NAME; 30 mg/kg), or acute ganglionic blockade (chlorisondamine; 30 mg/kg). Results are expressed as the percentage of basal lipolysis of fat cells from saline-treated control animals and are means ± S.E. (n = 8 per group; lipolytic experiments were performed in duplicate). Statistical comparisons were made by ANOVA and Sheffe’s post-hoc pairwise comparisons; *P <0.05, **P <0.01 versus control within the same pharmacologic pretreatment group, *P <0.05 versus leptin-treated NaCl-injected animals.
of leptin on adipocytes obtained from rats under acute ganglionic blockade achieved by chlorisondamine injection did not show differences in the lipolytic activity observed in control rats treated with leptin (Figure 4).

It is well known that a rise in cAMP resulting from either adenylate cyclase activation or phosphodiesterase inhibition stimulates lipolysis. In order to gain insight into the likely mechanisms implicated, lipolysis was stimulated in vitro in fat cells isolated from age- and weight-matched nontreated rats using a number of agents acting at different levels of the lipolytic pathway (Figure 5): at the β-adrenoceptor (isoproterenol); at the adenylate cyclase (forskolin); at the phosphodiesterase E (isobutylmethylxanthine [IBMX]); at the protein kinase A (dibutyryl-cyclic AMP [Bt2-cAMP]). To further validate the underlying assumption that NO is involved in the modulation of leptin-induced lipolysis, the effect of S-nitroso-N-acetyl-penicillamine (SNAP), a known NO donor, was assayed in vitro with leptin, isoproterenol, and combinations of the different lipolytic agents on fat cells isolated from age- and weight-matched nontreated control rats.

The lack of effect of leptin on isoproterenol-induced lipolysis in the in vitro assays adds further weight to the findings showing that leptin does not interfere with catecholamine-mediated lipolysis. A direct effect of leptin on adenylate cyclase appears unlikely because the hormone failed to reduce forskolin-induced lipolysis. Furthermore, the lack of effect on Bt2-cAMP-mediated lipolysis suggests that leptin does not interfere at the protein kinase A level either. Although a marked decrease in the release of glycerol was observed in IBMX-treated adipocytes after exposure to leptin, it did not reach statistical significance. However, the possibility that leptin may interfere at the phosphodiesterase level should not be completely ruled out.

Simultaneous presence of leptin and SNAP in the incubation medium of adipocytes isolated from Wistar rats exerted an additive effect on in vitro lipolysis compared with the effect elicited by the products acting

Figure 5. Schematic representation of the site of action of diverse pharmacologic agents at different levels of the lipolytic pathway. FSK = Forskolin, AC = adenylate cyclase, β AR = β-adrenoceptor, A1 = adenosine A1 receptor, ADA = adenosine deaminase, CPA = N6-cyclopentyladenosine, DPCPX = 8-cyclopentyl-1,3-dipropylxanthine, PTX = Pertussis toxin, G1 = inhibitory G-protein, GTP = guanosine 5′-triphosphate, GDP = guanosine diphosphate, ISO = isoproterenol, SNAP = S-nitroso-N-acetyl-penicillamine, PDE = phosphodiesterase E, Bt2-cAMP = dibutyryl-cyclic AMP, PKA = protein kinase A, IBMX = isobutylmethylxanthine, HSL = hormone-sensitive lipase.
individually ($P < 0.001$). Only SNAP exerted a statistically significant ($P < 0.001$) inhibitory effect on isoproterenol-stimulated lipolysis. Neither SNAP nor leptin modified forskolin-, Bt$_5$-cAMP-, and IBMX-stimulated lipolysis in lean rats.

The stimulatory effect of leptin, SNAP, and catecholamines has been studied in adipocytes of obese Zucker fa/fa rats to determine the effect of defective leptin receptor signaling on the stimulation of lipolysis. The lipolytic rate of white adipocytes obtained from fa/fa rats has been shown not to be responsive to the administration of leptin. However, addition of SNAP or isoproterenol to the incubation medium of fat cells of obese Zucker animals reportedly produces a marked lipolytic response, thus showing that the adipocyte preparations from these rats are not defective to other known lipolytic agents.

It can be concluded that NO may function as an important autocrine physiologic regulator signal controlling lipolysis by facilitating leptin-induced lipolysis and simultaneously being able to inhibiting catecholamine-induced lipolysis.

**Blood Pressure Homeostasis**

The presence of functional leptin receptors in brain regions and peripheral organs important in cardiovascular control such as heart, kidneys, and adrenals led investigators to suspect that leptin might affect blood pressure regulation. Intracerebroventricular as well as intravenous administration of leptin have been shown to increase both mean arterial pressure and heart rate. Furthermore, leptin administration reportedly increases sympathetic nerve activity to kidneys, adrenals, and brown adipose tissue. However, this generalized sympathoexcitation was not always followed by an increase in arterial pressure.

The finding of functionally competent OB-R in endothelial cells provided evidence that the endothelium was also a target for leptin action. The vascular endothelium is known to play a critical role in blood pressure homeostasis, in part through its ability to produce potent vasoactive factors, principal among these being the vasodilator NO. Some of my own research, therefore, has taken the approach of studying the potential role of NO in the leptin-induced effects on blood pressure regulation. Intravenous administration of leptin to Wistar rats was followed by a statistically significant ($P < 0.001$) dose-dependent increase in serum NO concentrations. Under NO synthesis inhibition, performed by l-NAME administration, leptin produced an increase in both systolic and diastolic blood pressure resulting in a sharp rise in mean arterial pressure. On the contrary, in the absence of sympathoactivation, achieved by pretreatment with the ganglion-blocking agent chlorisondamine, leptin administration significantly ($P < 0.01$) reduced both blood pressure and heart rate.

The effect of l-NAME injection in the setting of acute ganglionic blockade and leptin treatment was also studied to validate the underlying assumption that the hypotensive effect of leptin administration observed during ganglionic blockade is caused by the release of NO. Under these circumstances the inhibition of NOS by l-NAME blocked the leptin-mediated decrease in blood pressure during pharmacologically induced acute ganglionic blockade by chlorisondamine. Thus, leptin appears to have a balanced effect on blood pressure with a pressor response attributable to sympathetic activation and a depressor response attributable to NO release. This was the first study to show that leptin was involved in the control of vascular tone by simultaneously producing a neurogenic pressor action and an opposing NO-mediated depressor effect.

Obesity is associated with increased incidence of hypertension and cardiovascular mortality. However, the mechanisms that link obesity with high blood pressure have not been fully elucidated. The adipocyte-derived hormone, leptin, has been suggested to be implicated in obesity-related hypertension because it provides a link with well established risk factors like sympathetic activation, insulin resistance, increased sodium reabsorption, stimulation of the renin-angiotensin-aldosterone system, and endothelial dysfunction. Because leptin’s effects on NO synthesis appear to protect against the development of high blood pressure, it may be argued that if the vasculature is resistant to the actions of leptin, it may be involved in the development and maintenance of arterial hypertension. Therefore, a defect in the leptin system may contribute to hypertension as well as obesity. The increased incidence of hypertension observed in obesity may be explained by a hampered NO modulation of a compensatory hypertensive response. This possibility is supported by findings made in both animal models and humans. It has been reported that obesity-related hypertension is associated with attenuated arterial dilation. Furthermore, NOS activity has been shown to be decreased in obese Zucker rats compared with littermate controls and the JCR:LA corpulent rat shows a defective NO-mediated vascular relaxation. In humans an impaired endothelium-derived NO synthesis in obesity has been shown. In addition, an impaired NO-mediated vasodilation has been reported in elderly subjects with high blood pressure more commonly associated with old age.

Further studies on the relation between leptin and blood pressure homeostasis are currently underway focusing on the involvement of leptin in vascular reactivity in aortic rings and vascular smooth muscle cells (VSMCs) obtained from both Wistar and obese fa/f a rats.
The effect of leptin on angiotensin II–induced vascular responses is being examined in endothelium-denuded aortic rings using an organ bath system. Under physiologic conditions, angiotensin II interacting with AT1 receptors is known to increase the intracellular calcium concentrations of VSMCs, which leads to vasoconstriction. Our findings suggest that leptin reduces the angiotensin II–mediated isometric vasoconstriction in aortic rings and inhibits the rise in intracellular calcium concentrations induced by angiotensin II.51 Thus, leptin’s physiologic function may be related to opposing the vasoconstricting action of angiotensin II.

**Satiety Control**

The regulation of food intake has classically been divided into short- and long-term control systems.52 Afferent signals from the liver, the gastrointestinal tract, and the pancreas are known to participate in the short-term control of food intake by providing information to the central nervous system. Chemosensors for glucose, fatty acids, and amino acids inform the brain about the composition of the ingested nutrients, whereas mechanical receptors stimulated by the distension of the gastrointestinal wall provide information on the quantity of food consumed. Thus, the intraluminal food and digestion products as well as the stretching of the smooth muscle layers initiate the secretion of a plethora of hormones and peptides, which, via circulating signals and vagal afferents, reach the hypothalamus—the brain center responsible for satiety.

Recent advances in laparoscopy have renewed the interest in gastric banding techniques for the surgical treatment of carefully selected morbidly obese patients. Gastric banding represents a purely restrictive procedure designed primarily to reduce food intake.53 The adjustable gastric band is placed along the lesser curvature of the stomach and the phreno-gastric ligament. The band has an inflatable inner surface, which is connected by a kink-resistant tube to a subcutaneous injection reservoir. When fastened, the band forms a circular ring that allows adjustment of the gastric pouch outlet to the desirable size. Because the placement of an adjustable silicone band in order to obtain a reduced stomach pouch provides a change in the gastric anatomy and physiology (the aim being early satiety) the potential involvement of acute changes in leptin concentrations was explored. Specifically, following laparoscopic adjustable silicone gastric banding (LASGB) in male patients undergoing either LASGB or a comparable surgical procedure (as far as the time and kind of manipulations such as laparoscopic Nissen fundoplication) were investigated.

In the fundoplication group statistically significant decreases in glucose ($P < 0.05$), insulin ($P < 0.05$), and leptin ($P < 0.01$) concentrations were observed 24 hours after the presurgery values without significant changes in body weight. Similarly, the LASGB patients had a statistically significant ($P < 0.01$) decrease in glucose and insulin.54 However, leptin concentrations were found to be significantly ($P < 0.001$) increased 24 hours after the presurgery values without significant changes in either body weight or body fat. When comparing the percent change from presurgery values of both experimental groups it becomes evident that, as would be expected from the long fasting period, glucose and insulin concentrations fall in all patients. Leptin follows the same pattern of decrease in the fundoplication patients, whereas it significantly ($P < 0.001$) rises after the gastric banding manipulation. Interestingly, in all patients changes take place independently of significant variations in body weight or fat mass.

The role of insulin in *ob* gene expression and circulating leptin concentrations has been previously investigated and it has been shown that insulin administration increases *ob* gene expression in a dose-dependent manner.55 Consistent with those findings a statistically significant positive correlation between insulin and leptin values was observed in our fundoplication patients before surgery ($P < 0.04$).54 This significant correlation was maintained and even increased 24 hours after surgery ($P < 0.01$). Initially, the morbidly obese patients also exhibited a statistically significant correlation between both hormones ($P < 0.02$). After surgery, however, while insulin concentrations decrease, leptin departs from this pattern showing a pronounced increase.54 Thus, in bariatric patients the significant correlation between circulating leptin and insulin concentrations no longer holds up. These findings strongly suggest that the short-term increase observed in plasma leptin concentrations following LASGB might play a role in triggering an early satiety signal owing to the modification of the gastrointestinal anatomy and physiology.

**Conclusion**

Galileo was sentenced to life imprisonment commuted immediately to permanent house arrest under surveillance after denouncing the “Copernican heresy.” It has taken the Catholic Church more than 360 years to acknowledge their error: Pope Johannes Paulus II formally rehabilitated Galileo Galilei in 1992. Hopefully it will take some researchers less time to recognize the importance of the peripheral actions of leptin on whole-body physiology and pathology. The celebrated phrase, “Epur si muove” (nevertheless it moves), supposed to have been muttered by Galileo as he rose to his feet after abjuring on his knees before the Cardinal Inquisitors in Rome, was ultimately discovered on a fanciful portrait of Galileo in prison, executed in approximately 1640 by Murillo or one of his pupils at Madrid.

Insulin was discovered in the 1920s and after more
than 80 years new aspects are still being described. At this early juncture in the course of leptin research, much has been discovered. However, there is still much more that remains to be learned about leptin’s physiology and clinical relevance. Despite the reluctance of many researchers to grant the peripheral effects of leptin the relevance they deserve, and given leptin’s versatile and ever-expanding list of activities, additional and unexpected consequences of leptin are sure to emerge. The intense efforts underway on many different frontiers of leptin research will undoubtedly add more information to the already large body of knowledge.

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