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ISSN: 2332-8940 (Print) 2332-8959 (Online) Journal homepage: http://www.tandfonline.com/loi/ktmp20

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To cite this article: Angela M. Ramos-Lobo & Jose Donato Jr. (2017) The role of leptin in health and disease, Temperature, 4:3, 258-291, DOI: 10.1080/23328940.2017.1327003

To link to this article: http://dx.doi.org/10.1080/23328940.2017.1327003

Accepted author version posted online: 26 May 2017.
Published online: 26 May 2017.

TEMPERATURE
2017, VOL. 4, NO. 3, 258–291
https://doi.org/10.1080/23328940.2017.1327003

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COMPREHENSIVE REVIEW

The role of leptin in health and disease

Angela M. Ramos-Lobo and Jose Donato Jr.

Department of Physiology and Biophysics, Institute of Biomedical Sciences, University of São Paulo, São Paulo, SP, Brazil

ABSTRACT

Leptin is a master regulator of energy balance and body adiposity. Additionally, leptin exerts important control on glucose homeostasis, thermogenesis, autonomic nervous system and neuroendocrine axes. In metabolic diseases, such as obesity and diabetes mellitus, leptin signaling may be compromised, indicating the important role of this hormone in the etiology and pathophysiological manifestations of these conditions. In the present manuscript, we reviewed important concepts of leptin signaling, as well as about the effects of leptin on several biologic functions. We also discussed the possible therapeutic use of leptin administration and how our current obesogenic environment contributes to the development of leptin resistance. Our objective was to provide a comprehensive and state-of-the-art review about the importance of leptin to maintain the homeostasis and during pathological conditions.

ARTICLE HISTORY
Received 21 December 2016
Revised 27 April 2017
Accepted 2 May 2017

KEYWORDS
Hypothalamus; food intake; energy balance; obesity; diabetes

Leptin is a 16-kDa peptide hormone produced mainly by adipocytes, although other tissues and organs, such as mammary gland, ovary, skeletal muscle, stomach, pituitary gland and lymphoid tissue may produce lower amounts, possibly for local action.[1] Leptin is secreted proportionally to the mass of adipose tissue, thereby representing an important marker of energy storage. The adipocyte-derived leptin secretion displays a circadian profile, with highest levels at night and lowest levels at daytime in humans.[2] Leptin secretion also has a marked sexual dimorphism, with higher serum leptin concentration in women at any level of adiposity.[3] Several hormones modulate leptin secretion. For example, insulin induces leptin secretion,[4,5] whereas cortisol displays an inverse circadian rhythm.[6]

Remarkably, the physiologic role of leptin started to be studied before the discovery of leptin itself. This unusual situation was possible because spontaneous mutations generated leptin and leptin receptor (LepR; also known as Ob-R) deficient mice decades before the identification of their mutations.[7-9] The first description of the leptin deficient mouse occurred in 1950 and this mouse strain was named as *ob/ob* because of its morbid **ob**ese phenotype.[10] In 1966, another mutation was described in an inbred strain of mouse that was characterized by a metabolic disturbance resembling diabetes mellitus. Consequently, homozygous mutants were named as *db/db* because they carried the **d**ia**b**etes gene.[9] Years later, Coleman and colleagues through parabiosis experiments came to the conclusion that the obesity of *ob/ob* mice was likely caused because they lacked a circulating factor, whereas the phenotype of *db/db* mice was possibly caused by the lack of the receptor for that factor.[7,8,11-13] It turned out that Coleman and colleagues were right, and in 1994 Jeffrey Friedman's group discovered that the *ob* gene encodes the hormone leptin.[14] In two separated papers, the *Lepr* gene was identified and demonstrated that LepR is encoded by the *db* gene.[15,16]

Growing literature shows that not only leptin is a master regulator of energy balance, but it also modulates glucose homeostasis, neuroendocrine axes, autonomic nervous system, memory, neural plasticity, and other biologic functions. The objective of this manuscript is to provide a comprehensive review about the effects of leptin on several biologic functions, its mechanisms of action and how leptin is related to several diseases, such as obesity and diabetes mellitus.

CONTACT Jose Donato Jr. jdonato@icb.usp.br Department of Physiology and Biophysics, Institute of Biomedical Sciences, University of São Paulo, Av. Prof. Lineu Prestes, 1524, São Paulo, SP 05508-000, Brazil.

The biology of leptin

Leptin receptor and signaling pathways

Leptin acts by binding to its membrane receptor, which is expressed in many tissues. Through an expression cloning strategy, six LepR isoforms were identified (LepRa-f).[15] Although all six LepR isoforms share a common extracellular ligand-binding domain at the N-terminus, they differ in their intracellular domain, and therefore in their physiologic role. LepRe lacks the transmembrane domain, representing a soluble LepR isoform. Thus, LepRe is a leptin-binding protein and possibly regulates leptin biologic activity by removing it from circulation.[17] LepRa, a short isoform of the receptor, is abundantly expressed in the choroid plexus, and has been hypothesized to be implicated in leptin transport into the central nervous system (CNS) through the blood–brain barrier (BBB).[18] Only the long isoform (LepRb or Ob-Rb) contains all intracellular motifs required for complete activation of the intracellular signaling pathways. LepRb is predominantly expressed in the CNS and is essential for leptin action.[19-22] Consequently, this isoform is responsible for the main biologic effects of leptin. The obese mouse model known as *db/db* lacks exclusively the LepRb, and its phenotype is similar to mutants that have no LepR isoforms (db^{3J} mutation).[23] LepR belongs to the family of class 1 cytokine receptors with many similarities to the interleukin (IL)-6 receptor. This type of receptor does not contain intrinsic tyrosine enzymatic activity but signals via an associated tyrosine kinase protein from the Janus kinase family (JAK) (Fig. 1). When leptin binds to LepRb, JAK2 is recruited, activated and promotes autophosphorylation and phosphorylation of three tyrosine residues of LepRb (Y985, Y1077 and Y1138). These phosphorylated tyrosine residues act as docking sites for downstream signaling molecules, representing a Src homology 2 (SH2)-binding motif that recruits specific SH2-containing effector proteins to mediate subsequent intracellular signaling.[24] The major signaling pathway recruited by leptin is the signal transducer and activator of transcription 3 (STAT3), which depends on the phosphorylation of Y1138.[25,26] STAT3 is a transcription factor and after phosphorylation STAT3 migrates to the nucleus where the expression of target genes will be transcriptionally regulated. When the Y985 residue of LepR is phosphorylated, Src homology 2-containing tyrosine phosphatase (Shp2; encoded by *Ptpn11* gene) is recruited to LepR, leading to the activation of extracellular signal-regulated kinases (ERK) signaling pathway (Fig. 1).[24] Y985 is also a binding site for the suppressor of cytokine signaling 3 (SOCS3), which is a protein that exerts inhibitory effects on leptin signaling. Since SOCS3 transcription is dependent on leptin signaling through STAT3, it exerts its inhibition via a classic negative feedback way. Finally, phosphorylation of Y1077 recruits STAT5. Although the activation of STAT5 is mainly dependent on the Y1077 residue, STAT5 can also be activated by phosphorylation on Y1138.[27] STAT5 pathway is more related to metabolic functions controlled by other cytokines like growth hormone (GH) and prolactin.[28] However, STAT5 pathway mediates some of the effects of leptin on the regulation of energy balance and reproduction (Fig. 1).[28,29]

Another signaling pathway activated by leptin is the phosphatidylinositol 3-kinase (PI3K). PI3K is a major signaling pathway for insulin and other growth factors in peripheral tissues as well as the CNS.[30] JAK2 phosphorylates insulin receptor substrates (IRS) leading to PI3K activation (Fig. 1). Unlike the JAK/STAT pathway, which acts through gene expression regulation, PI3K can produce fast cellular responses by promoting changes in ion channels and thereby in cell activity.[31]

For many years it was challenging to identify leptin-responsive cells. Antibodies against LepR produce poor staining frequently leading to false-positive or false-negative results.[32,33] The use of radiolabeled leptin to identify binding sites was not able to identify many brain areas that also contain LepR expression.[15] Furthermore, the LepR mRNA levels are commonly low in many brain areas, which makes it difficult the precise identification of LepR-expressing cells.[34-39] Due to these limitations, many studies begun to identify leptin-responsive cells via the activation of its signaling pathways. Therefore, STAT3 phosphorylation (pSTAT3) after an acute leptin stimulus became a popular marker to identify leptin-responsive cells (Fig. 2).[25,40-42] Additionally, STAT3 phosphorylation is also widely used as a way to evaluate leptin sensitivity.[43-46]

The physiologic role of leptin

The word leptin is derived from the Greek root leptós that means thin. The choice of Friedman's group to name the hormone leptin was based on the first

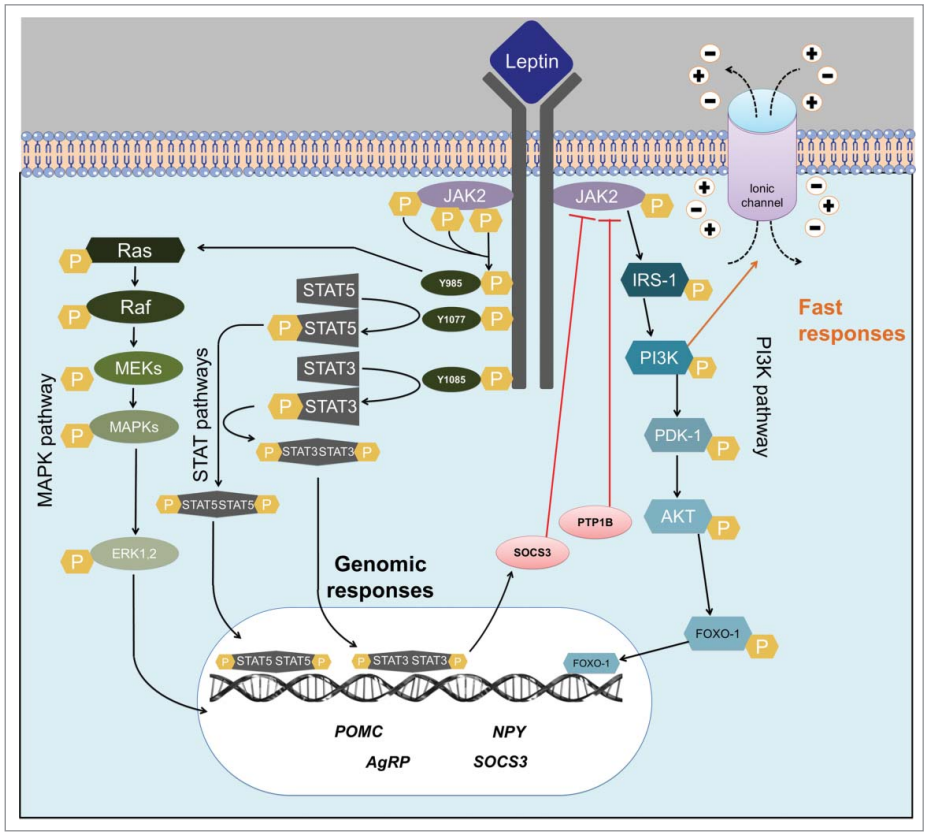

Figure 1. Leptin signaling pathways. Scheme summarizing the main intracellular pathways activated by the long-form of leptin receptor (LepR). Abbreviations: PI3K, phosphatidylinositol-3-kinase; IRS, insulin receptor substrate; JAK2, janus kinase 2; STAT, signal transducer and activator of transcription; SOCS3, suppressor of cytokine signaling-3; PTP1B, phosphotyrosine phosphatase 1B; SHP-2, src-homology-2 containing phosphotyrosine phosphatase 2; MAPK, mitogen-activated-protein-kinase; Raf, raf proto-oncogene serine/threonine-protein kinase; Ras, family of small GTPase; ERK1/2, Extracellular signal-regulated kinases; MEK, mitogen-activated protein kinase kinase; PDK-1, phosphoinositide-dependent kinase-1; AKT, ak strain transforming/protein kinase FOXO-1, forkhead box protein O1.

studies that infused leptin in mice and observed a significant reduction in their body weight and adiposity.[47] Although these earlier studies may indicate that leptin could have an application in the treatment of obesity, latter evidence demonstrated that most cases of obesity are characterized by excess of leptin and leptin resistance.[48] Only in rare cases of obesity caused by congenital deficiency (similar to the *ob/ob* model) leptin treatment was a useful tool to revert obesity.[49,50]

The deficiency of leptin or LepR produces a very characteristic phenotype of hyperphagia, morbid obesity and insulin resistance.[51] As described above, leptin treatment in *ob/ob* mice reversed their obese phenotype, which led to the conclusion that the physiologic role of leptin is to reduce the body weight and food intake.[47] However, over the years, many studies have shown that leptin's role is in fact much more complex, given its participation in many other physiologic functions, from neuronal development and plasticity, memory and cognition, glucose homeostasis, reproduction and metabolic programming, which will be detailed across this review.[52,53] For some authors, leptin's biologic role is not to make an animal thin, as originally described, but to act as a signal to the brain to convey the energy status of the body and thereby modulate energy-demanding functions to maintain homeostasis.[54] In response to fasting, leptin levels decrease intensively, more than expected by the changes in body adiposity. This rapid reduction in leptin levels coordinates profound alterations in the metabolism and neuroendocrine axes that will save energy to ensure survival during conditions of negative energy balance. Falling in leptin levels can also trigger behaviors that will increase the search for food. When leptin is supplemented in fasted individuals, starvation-induced changes are attenuated.[55-57] Therefore, leptin's main physiologic role is likely to promote survival, via neuroendocrine, behavioral and metabolic adaptations to preserve energy and increase food intake in situations of negative energy balance.

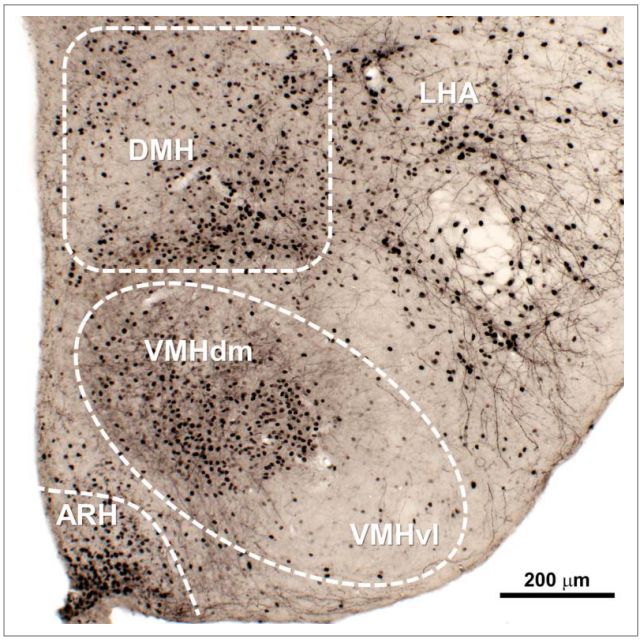

Figure 2. Distribution of leptin responsive neurons in the mouse mediobasal hypothalamus. Leptin-responsive cells could be visualized by the phosphorylation of STAT3 (black nuclear staining) 90 min after an acute peritoneal injection of mouse recombinant leptin (10 μg/g body weight). Abbreviations: ARH, arcuate nucleus of hypothalamus; DMH, dorsomedial nucleus of hypothalamus; LHA, lateral hypothalamic area; VMH, ventromedial nucleus of hypothalamus; VMHdm, dorsomedial part of the VMH; VMHvl, ventrolateral part of the VMH.

Because in nature is more common the need of survival mechanisms in situations of undernutrition, leptin elicits more robust physiologic responses when its levels are low (conveying a signal of low levels of energy stocks), differently than when its levels are increased (like in obesity), a rare situation in nature (reviewed in Leibel[58]).

Food intake

Leptin plays a pivotal role regulating food intake. *Ob/ob* and *db/db* mice exhibit a marked hyperphagic behavior.[47] Leptin infusion, either peripherally or centrally, produces a significant suppression in food intake in *ob/ob* and wild-type animals, but not in *db/db* mice.[47,51,59,60] A robust voluntary reduction in energy intake is also achieved in leptin-deficient humans chronically treated with leptin.[50,61] Several intracellular signaling pathways mediate the effects of leptin on food intake. While disruption of LepR/STAT3 pathway produces hyperphagia, pharmacological or genetic disruption of the PI3K pathway prevents the suppression of food intake in the 24 h following leptin administration.[62,63]

Although different neuronal populations are likely responsible to mediate leptin's effects on food intake, the arcuate nucleus of the hypothalamus (ARH) is certainly an important area.[64] In the ARH, leptin acts at least in two distinct neuronal populations to affect food intake. Neurons that co-express the proopiomelanocortin (POMC) prohormone and the cocaine and amphetamine regulated transcript (CART) are responsive to leptin.[36,65] ARH POMC/CART neurons are activated by leptin and these cells normally inhibit food intake.[66-68] This occurs because CART has anorexigenic effects,[69] whereas POMC is cleaved in different peptides, including α-melanocyte-stimulating hormone (α-MSH), which is able to activate melanocortin receptors 3 and 4 (MC3R/MC4R) leading to increased satiety.[70] MC4R ablation reproduces many of the metabolic aspects observed in *db/db* mice, including their morbid obesity and hyperphagia.[71] Anatomically, POMC neurons are found predominantly in the lateral ARH (Fig. 3A).[72] On the other hand, located in the ventromedial ARH (close to the third ventricle and median eminence), neurons that co-express the neuropeptide Y (NPY), the agouti-related protein (AgRP) and the amino acid GABA are inhibited by leptin (Fig. 3A).[73] The NPY/AgRP/GABA neurons are potent inducers of food intake due to several reasons.[74,75] NPY is one of most powerful orexigenic neuropeptides as demonstrated by the robust feeding produced by intracerebroventricular NPY injections.[76] AgRP is an inverse agonist of MC3R/MC4R. Consequently, AgRP blocks the capacity of α-MSH to activate MC3R/MC4R, which also leads to an increase in food intake.[70,77] Finally, several pieces of evidence also indicate that the inhibitory GABAergic transmission of these neurons is important to modulate neural circuits involved in feeding behavior.[75,78,79] Therefore, via a relationship of antagonism,[77] POMC/CART and NPY/AgRP/GABA neurons form the central melanocortin system controlling the activity of second-order neurons that typically express the MC4R. It is worth mentioning though that although leptin exerts important effects on POMC/CART and NPY/AgRP/GABA neurons,[80] many pieces of evidence indicate that leptin must act on multiple neuronal populations and neurocircuits to properly regulate food intake and energy balance. For instance, disruption of LepR expression exclusively in POMC/CART or NPY/AgRP/GABA neurons produces relatively modest effects on food intake and energy

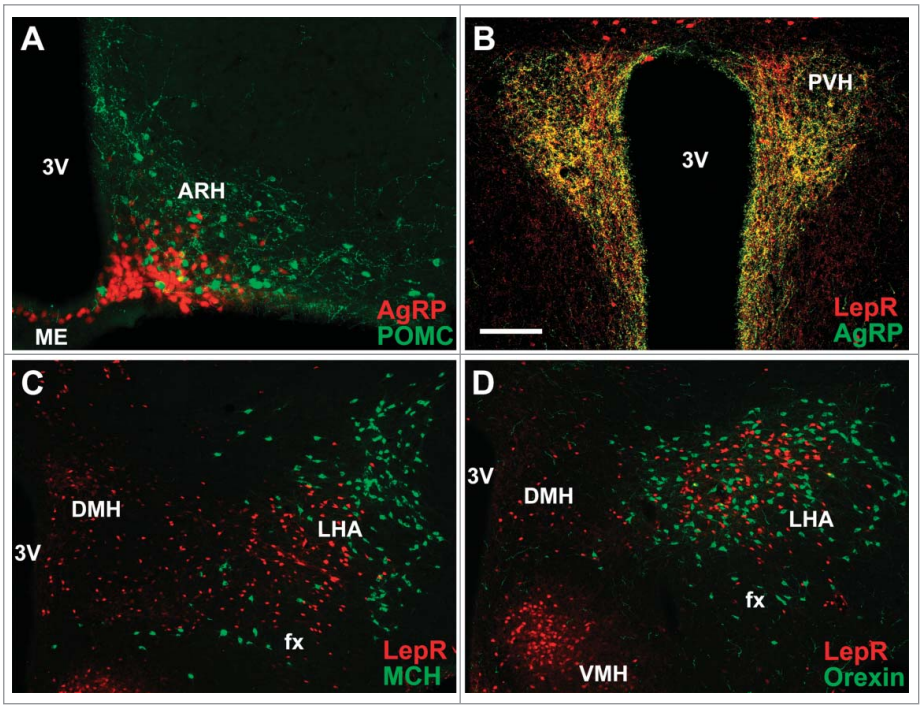

Figure 3. Hypothalamic distribution of key neuronal populations involved in the regulation of energy balance. (A) AgRP neurons in the ARH are located close to the third ventricle and median eminence, whereas POMC neurons are predominantly in the lateral ARH. POMC neurons were visualized by immunostaining β-endorphin peptide, while AgRP neurons were visualized using a reporter mouse that express the tdTomato fluorescent protein under the *Agrp* promoters. (B) PVH receives dense projections from LepR/AgRP neurons. Green fibers were visualized by immunostaining AgRP peptide, whereas axons from LepR-expressing neurons were visualized using a reporter mouse that express the tdTomato fluorescent protein under the *Lepr* promoters, as previously shown.[86] Note the extensive co-localization (yellow color). (C, D) MCH (C) and orexin (D) neurons represent a segregate neuronal population in the LHA and do not express LepR. MCH and Orexin neurons were immunostained using specific antisera, whereas LepR-expressing neurons were visualized using a reporter mouse that express the tdTomato fluorescent protein under the *Lepr* promoters. Abbreviations: 3V, third ventricle; ARH, arcuate nucleus of hypothalamus; DMH, dorsomedial nucleus of hypothalamus; fx, fornix; LHA, lateral hypothalamic area; ME, median eminence; PVH, paraventricular nucleus of the hypothalamus; VMH, ventromedial nucleus of hypothalamus. Scale bar: A–B = 100 μm; C–D = 200 μm.

balance,[81,82] which markedly contrasts with the profound impact in the energy homeostasis caused by the complete ablation of NPY/AgRP/GABA neurons (via diphtheria toxin) or by the lack of MC4R.[71,83]

The paraventricular nucleus of the hypothalamus (PVH) is an important brain structure that receives dense projections from either POMC/CART or NPY/AgRP/GABA neurons (Fig. 3B).[84-86] Expression of MC4R exclusively in PVH neurons can rescue the increased food intake observed in *Mc4r* null mice.[84] During calorie-restricted conditions, ARH NPY/AgRP/GABA neurons are strongly activated as demonstrated by an increased intrinsic action potential frequency.[87] The increased activity of ARH NPY/AgRP/GABA neurons is mediated by the decreased levels of anorexigenic hormones, such as leptin, while the orexigenic hormone ghrelin activates these cells.[88] However, recent evidence also indicates that PVH neurons can provide a potent excitatory input to ARH NPY/AgRP/GABA neurons during fasting, representing another way to produce hunger in calorie-restricted conditions.[89,90] Consequently, there is a reciprocal regulation between ARH and PVH neurons to control food intake.

Other brain structures also interact directly to ARH neurons to control feeding. For example, NPY/AgRP/GABA neurons project to the parabrachial nucleus (PBN) which in turn regulates neurons in the amygdala to control food intake. This circuit is especially important in conditions when it is unfavorable to eat, such as after severe overfeeding or during illness.[78,91,92] The lateral hypothalamic area (LHA) receives projections from different populations of LepR-expressing neurons, and it is also a critical structure that regulates feeding.[93] Neurons that express the neuropeptides melanin-concentrating hormone (MCH) or orexin (also known as hypocretin) are found in the LHA and these cells stimulate feeding, although they do

not express the LepR (Fig. 3C and D).[94] On the other hand, LepR expression in the LHA is found in neurotensin-positive neurons, and LepR ablation in these cells increases food intake.[95] Leptin acts in LHA neurotensin neurons leading to an inhibition of orexin neurons.[96] Neurotensin receptor-1 disruption promotes hedonic feeding.[97]

The ability of leptin to regulate feeding depends on several neuronal populations and neurocircuits. Pharmacogenetic activation of LepR-expressing neurons in the median preoptic area (MPO) induces a robust suppression of food intake in mice.[98] Dopamine neurons in the ventral tegmental area (VTA) express the LepR as well.[99,100] Direct administration of leptin to the VTA decreases food intake.[99] Additionally, long-term RNAi-mediated knockdown of LepR in the VTA strengthens the sensitivity to highly palatable food and increases food intake.[99] Leptin also modulates the activity of urocortin 1 neurons in the Edinger–Westphal (EW) nucleus.[101] Since urocortin 1 produces anorexigenic effects, this particular neuronal population may mediate some of the leptin's effects on food intake.[101] LepR expression is also found in brainstem neurons, including cells of the nucleus of the solitary tract (NTS),[102-104] which is an important sensory relay from the upper gastrointestinal tract. LepR-expressing cells in the NTS co-express different neurochemical markers including POMC, cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1).[105] Selective inactivation of LepR in Phox2b positive cells causes LepR deletion in NTS GLP-1 neurons.[106] This genetic manipulation generates mice that display increased food intake after fasting, indicating that leptin action on GLP-1 neurons also controls food intake.[106] In line with these findings, RNAi-mediated knockdown of LepR in NTS resulted in hyperphagia for chow, high-fat or high-sucrose diets, leading to an increase in body weight and adiposity.[107] Recent evidence also suggests that leptin signaling in non-neuronal cells regulates feeding. Astrocyte-specific LepR deficiency leads to increased food intake.[108] Overall, leptin possibly acts in neurons located in the ARH, LHA, MPO, VTA and NTS, as well as in non-neuronal cells to control different aspects of feeding behavior. Fig. 4 summarizes the participation of different brain nuclei in the multiple physiologic functions regulated by leptin signaling.

Energy expenditure and thermogenesis

It is well known that leptin affects the energy balance not only through the modulation of food intake, but it also has potent effects on energy expenditure. *Ob/ob* and *db/db* mice have high metabolic efficiency because of low energy expenditure.[51,109] These defects can be corrected by leptin replacement only in *ob/ob* mice.[51] Similarly to food intake, the regulation of energy expenditure by leptin depends on multiple neuronal populations. Conditional deletion of LepR from POMC cells leads to obesity without affecting food intake.[81] Actually, these mutants exhibit a tendency toward low energy expenditure.[81] In accordance with these findings, selective expression of LepR only in POMC cells produces no change in food intake, while the low energy expenditure observed in LepR-deficient mice is significantly rescued.[110] Ablation of LepR only in AgRP neurons or simultaneously in POMC and AgRP cells does not affect food intake in adult mice, although these animals develop obesity, suggesting an alteration in energy expenditure.[82] Accordingly, the

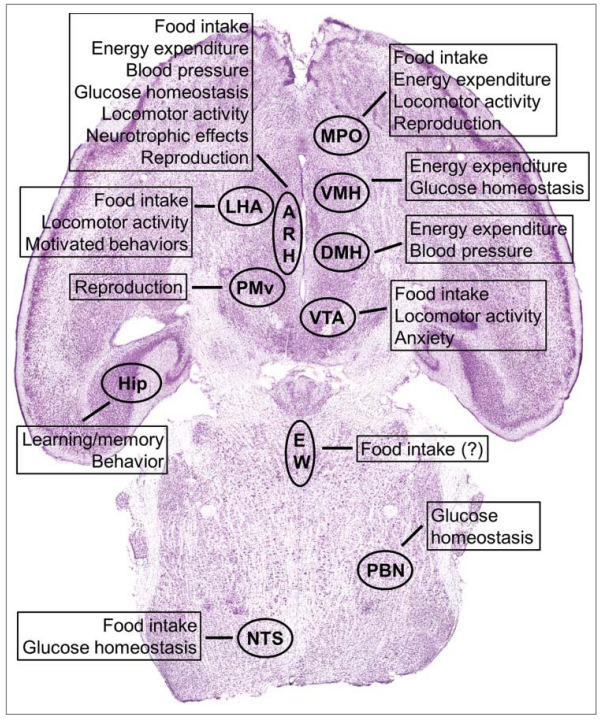

Figure 4. Brain distribution of LepR-expressing neurons and their known biologic functions regarding leptin signaling. Abbreviations: ARH, arcuate nucleus of the hypothalamus; DMH, dorsomedial nucleus of the hypothalamus; EW, Edinger–Westphal nucleus; Hip, hippocampus; LHA, lateral hypothalamic area; MPO, medial preoptic area; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; PMv, ventral premammillary nucleus; VMH, ventromedial nucleus of the hypothalamus; VTA, ventral tegmental area.

low energy expenditure of *ob/ob* mice is partially improved in NPY-deficient animals.[111]

The ventromedial nucleus of the hypothalamus (VMH) is also an important structure involved in the energy balance regulation. Since steroidogenic factor-1 (SF1)-positive neurons are found only in the VMH, SF1 became a marker to induce genetic manipulations in this nucleus. Mice carrying a selective deletion of LepR in SF1 cells show a similar degree of obesity compared with POMC specific LepR ablation.[112,113] Notably, this obese phenotype occurs in the absence of changes in food intake. However, SF1 specific LepR knockout mice exhibit an attenuated thermogenic response to high-fat diet (HFD).[112,113] Several reports have demonstrated that leptin action in the dorsomedial nucleus of the hypothalamus (DMH) increases sympathetic tone to brown adipose tissue (BAT) and interscapular BAT temperature.[114-116] Acute cold exposure induces c-Fos in DMH LepR-expressing neurons.[115] Disruption of LepR selectively in DMH neurons causes obesity, reduces the energy expenditure and blocks thermogenic responses to leptin, without affecting food intake.[116,117] Besides regulating food intake, MPO LepR-expressing neurons are also involved in temperature-dependent body weight homeostasis.[98,115] This specific population innervates sympathetic BAT circuits.[115] Activation of MPO LepR-expressing neurons suppresses energy expenditure leading to a reduction in body temperature.[98]

It is worth mentioning that leptin can regulate energy expenditure not only by changes in autonomic nervous system, but also through neuroendocrine mechanisms. Thyrotropin-releasing hormone (TRH) neurons in the PVH are master regulators of the thyroid gland function, whose hormones exert profound impact in the cellular metabolism and consequently in energy expenditure. PVH TRH neurons receive projections from ARH LepR-expressing neurons (Fig. 3B).[118,119] During calorie-restricted conditions, the reduction in leptin levels coordinates endocrine and metabolic changes to save energy, which includes suppression of TRH, thyroid-stimulating hormone and thyroid hormones.[55,57] Infusion of either α-MSH or CART is able to prevent fasting-induced suppression of TRH mRNA levels in the PVH.[118-121] Therefore, leptin signaling in ARH neurons controls neuroendocrine cells of the PVH to regulate thyroid axis according to nutritional status.

Ob/ob mice exhibit a reduced body temperature, and in the past this phenotype was thought to be the result of lower energy expenditure.[122-124] However, recent findings indicate that leptin actually acts centrally to modulate thermoregulatory mechanisms raising the defended body temperature and/or reducing thermal conductance.[125,126] BAT is the main organ that produces heat by increasing energy expenditure. BAT expresses the uncoupling protein 1 (UCP1), a mitochondrial channel that uncouples the proton motive force of the respiratory chain from ATP production to heat production.[127] BAT is innervated by the sympathetic nervous system and the activation of UCP1 is mainly regulated by β3-adrenergic receptors.[128] Rats treated with leptin showed increased oxygen consumption and UCP1 mRNA expression, and this response is elevated after fasting.[129] In the past, it was believed that BAT's function was critical only in small rodents; however, nowadays we known that BAT is present and functional in adult humans as well and became a potential target for obesity treatment.[130] Genetic approaches enhancing leptin and insulin signaling in POMC neurons increase white adipose tissue browning and energy expenditure, conferring a protection against diet-induced obesity (DIO).[131] In addition, the absence of hypothalamic insulin and leptin receptors maintains a lower body temperature (at 20–22 °C) than when either of the receptors is removed independently.[132]

Since endotherms need to maintain their internal body temperature, a process that demands large amounts of energy, during fasting conditions small endotherms may enter a status of daily torpor, thereby suppressing their metabolic rate together with a fall of core temperature lasting for a period of several hours.[133] This event can also be present in situations of low energy sources or in in a low temperature ambient.[134] Evidence in literature shows that the critical factor that determines the moment of entering torpor is the achievement of a critical low body mass, which drives the decrease in daytime core temperature in both DIO and lean mice facing fasting.[135]

Since leptin's structure resembles a cytokine, it is not surprising that leptin has an important role in the immune system. Leptin levels increase during infections, inflammations or lipopolysaccharide (LPS) exposure as a part of the host immune response (Fig. 5). This change is mediated by IL1-β.[136] Evidence in animal models has demonstrated

that systemic inflammation caused by LPS leads to increased circulating leptin,[137,138] and the peak of leptin is preceded by an increase in tumor necrosis factor (TNF)-α, which by itself is also capable of increasing leptin circulating levels.[139] Systemic inflammation and sepsis are closely related to changes in body temperature, both in animals and humans.[140,141] Systemic inflammation is commonly followed by fever; however, in some situations it can evoke hypothermia.[142] In animals, the response to LPS depends on the dose given and the environment temperature. In thermoneutral environment, fever is the predominant response. Low doses of LPS induce monophasic fever, which turns into polyphasic fever when the dose is increased.[143] However, if a high dose of LPS is given in a low temperature environment, the response changes to hypothermia.[144] Evidence shows that fever is a predominant response for mild stimuli, whereas hypothermia is a natural response for stronger inflammatory injuries.[145] A major regulator for these responses is TNF-α that, depending on the dose, can be thermogenic or cryogenic. LepR KO rats (Koletsky *f/f*) have the same fever response to low doses of LPS as wild-type rats, but when treated with high doses of LPS express a severe hypothermia that lasts longer, associated with increased levels of TNF-α. A possible explanation for the TNF-α increase in LepR KO rats is the fact that they are unable to fully activate their hypothalamic-pituitary-adrenal axis which has anti-inflammatory actions in response to LPS, and therefore leptin seems to be important to recover from hypothermia induced by LPS.[146] Further evidence for this point is that *ob/ob* mice do not activate their hypothalamic–pituitary–adrenal axis in response to LPS, compared with wild-type animals.[147,148] In leptin responsive animals, stimuli that normally evoke highly febrigenic responses in fed animals result in hypothermia or low fever when the animals are fasted and they show elevated TNF-α levels.[149-152] This is suggested to be related to low levels of leptin in fasted animals, because of the similar response observed in leptin-irresponsive rats (Koletsky *f/f*) (reviewed in refs.[153,154]).

In DIO rats, in which leptin levels were blocked with specific antiserum, the later phases of the fever response were attenuated. Thus, leptin was suggested to play an important role modulating the late phase of the fever response to LPS in obese animals.[155] Higher levels of circulating leptin in old rats were associated with enhanced duration and degree of symptoms after LPS injection together with prolonged fever compared with young rats, showing that leptin has a role in age-dependent febrile responses to inflammation.[156]

Another phenomenon that can alter the regulation of body temperature is the psychological stimulated hyperthermia, both in animals and humans. This condition increases BAT thermogenesis[157] and can be diminished by systemic administration of a β3-adrenoceptor antagonist in rats.[158] However, the physiologic mechanisms involved in the hyperthermia induced by psychological stress are different from those involved in LPS-induced fever.[159]

In summary, leptin signaling in the ARH (POMC and AgRP/NPY neurons), VMH, DMH and MPO modulates the autonomic nervous system or endocrine axes leading to changes in energy expenditure and thermogenesis. Therefore, the powerful effects of leptin on the energy balance depend on a simultaneous regulation of food intake and energy expenditure. Furthermore, there is also evidence that leptin regulates immune responses, as well as body temperature through the modulation of central

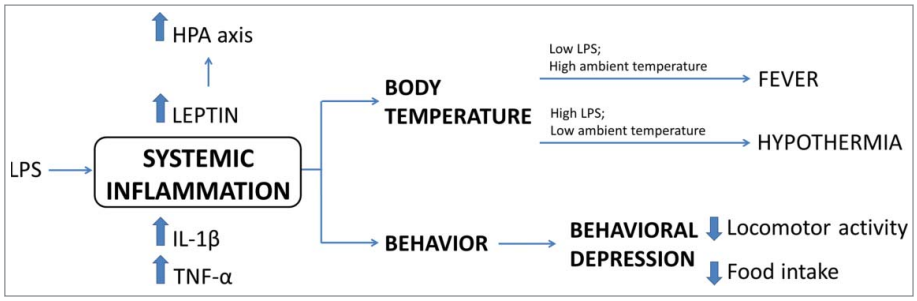

Figure 5. Physiological responses to systemic inflammation. Scheme summarizing changes in body temperature, behavior and secreted factors after LPS-induced inflammation as well as the leptin's role in the recovery of febrigenic or hypothermic processes.

thermoregulatory mechanisms. Fig. 5 summarizes the physiologic responses to systemic inflammation and the role of leptin in the recovery of febrigenic or hypothermic processes.

Regulation of cardiovascular functions via autonomic nervous system

Recent reports indicate that DMH LepR-expressing cells also control blood pressure.[160] Interestingly, leptin or LepR deficiency protects against hypertension, despite the morbid obese phenotype caused by these mutations. Additionally, increased leptin levels in DIO promotes increased blood pressure in rodents, which is an effect likely mediated by DMH neurons.[114,160] The same protection against obesity-induced hypertension is observed in MC4R deficient mice, which indicates the involvement of the central melanocortin system in this dysfunction.[161] Accordingly, MC4R expression in cholinergic neurons, which include sympathetic and parasympathetic preganglionic neurons, restores obesity-associated hypertension in MC4R deficient mice.[162] Additionally, exclusive MC4R expression in cholinergic neurons is sufficient to normalize the energy expenditure abnormalities exhibited by MC4R deficiency, without affecting food intake.[163] Thus, leptin acts via the melanocortin system and DMH LepR neurons to regulate blood pressure through the modulation of the autonomic nervous system.[160,161,164]

Glucose homeostasis

Glucose homeostasis is regulated by brain leptin signaling, independently of its effects on adiposity. For example, leptin infusion at low doses that does not affect body weight is able to correct the hyperglycemia and hyperinsulinemia of *ob/ob* mice.[51] Additionally, genetic manipulation that increases leptin sensitivity in LepR-expressing cells does not prevent DIO, but protects mice from obesity-induced insulin resistance.[165] Since adiposity plays a major role contributing to insulin resistance, it is sometimes difficult to determine whether leptin signaling in a specific brain structure directly controls glucose homeostasis or if the observed effects are secondary to changes in body weight and adiposity. However, there is solid evidence that some specific neuronal populations are particularly important to mediate leptin's effects on glucose homeostasis. Unilateral LepR reactivation in the ARH of otherwise LepR-deficient mice produces modest effects on body weight and adiposity, although this manipulation causes marked improvements in hyperinsulinemia and blood glucose levels.[64] Leptin signaling in POMC neurons probably explains much of these effects, since selective expression of LepR only in POMC cells also produces robust improvements in the hyperinsulinemia and hyperglycemia of LepR-deficient mice, even though it causes small effects on body weight and adiposity.[110,166] In accordance with the role of the central melanocortin system controlling glucose homeostasis, Rossi et al.[163] found that, compared with MC4R deficient mice, re-expression of MC4R in cholinergic neurons (autonomic sympathetic and parasympathetic preganglionic neurons) produces expressive improvements in glucose control, insulin sensitivity and insulin-mediated suppression of hepatic glucose production. Interestingly, restoration of MC4R expression in the dorsal motor nucleus of the vagus (DMX), which is composed of parasympathetic preganglionic neurons, attenuates the hyperinsulinemia, but does not normalize the hyperglycemia of MC4R deficient mice, suggesting that the melanocortin system probably influences both sympathetic and parasympathetic branches to regulate different aspects of glucose homeostasis.[162,163]

There is some evidence that leptin signaling in VMH neurons also regulates glucose homeostasis. For example, selective inactivation of SOCS3 in SF1 cells increases leptin sensitivity, leading to an improvement of glucose homeostasis, without affecting body weight.[167] VMH is a key area involved in counter-regulatory responses to hypoglycemia.[168] Excitatory glutamatergic transmission from VMH neurons is required to prevent fasting-induced hypoglycemia.[169] A neurocircuit between brainstem and VMH was recently described to control counter-regulatory responses to hypoglycemia. In this circuit, leptin-responsive cells in the lateral PBN express CCK and are inhibited by glucose. Leptin inhibits PBN CCK neurons and inactivation of LepR in CCK cells enhances counter-regulatory responses to hypoglycemia.[170,171] PBN CCK neurons project to and regulate VMH SF1 cells via CCK release, and this neurocircuit is both necessary and sufficient for triggering counter-regulatory responses to hypoglycemia.[168,170,171] Thus, several pieces of evidence indicate that leptin controls

sympathetic and parasympathetic nervous systems via the melanocortin system to regulate glucose homeostasis. PBN CCK neurons are also directly regulated by leptin to modulate counterregulatory responses to hypoglycemia via connections with VMH SF1 neurons.

Reproduction

Calorie-restricted conditions also suppress the reproductive axis and these effects are leptin dependent.[55,57,172,173] Several studies investigated potential brain areas that could mediate leptin's effects on reproduction. Although LepR-expressing cells are located nearby gonadotropin-releasing hormone (GnRH) neurons, there is no direct effect of leptin on these cells.[174] Consequently, interneurons are necessary to convey leptin signal to GnRH neurons. Kisspeptin (peptide encoded by the *Kiss1* gene) expressing neurons are required to sense estrogen levels to regulate GnRH neurons.[175] Although earlier reports identified LepR mRNA expression in Kisspeptin neurons,[176] more recent studies found a very limited LepR expression in these cells.[177,178] Additionally, selective manipulation of LepR in Kisspeptin cells produced no significant impact on reproduction.[177,179] On the other hand, neurons in the ventral premammillary nucleus (PMv) exhibit an abundant expression of LepR and play a critical role mediating leptin's effects on reproduction.[180,181] PMv neurons project to GnRH cell bodies and fibers that reach median eminence, exerting an excitatory effect through their glutamatergic transmission.[179,182,183] Excitotoxic lesions of the PMv in adult female rats disturb estrous cycle, the activation of GnRH neurons during the proestrus and GnRH and Kiss1 mRNA expression at the night of proestrus.[184,185] PMv-lesioned rats also failed to show the stimulatory effects of leptin on luteinizing hormone (LH) secretion during fasting.[185] The most substantial evidence that PMv neurons mediate the effects of leptin on reproduction came from studies that induced LepR-expression only in PMv neurons of otherwise LepR-deficient mice. In this study, unilateral re-activation of LepR in the PMv was sufficient to restore fertility, despite a complete absence of changes in body weight and food intake.[179]

Besides the PMv, MPO LepR-expressing neurons also regulate reproduction. These cells are found close to GnRH neurons and release nitric oxide (NO).[103,186] Neuronal NO synthase (nNOS) knockout mice are unable to show the stimulatory effect of leptin on LH secretion, and pharmacological nNOS inhibition in the preoptic area prevents the restoration of fertility in leptin-treated *ob/ob* female mice.[186] NPY/AgRP neurons are also important targets of leptin to regulate reproduction. *Db/db* mice carrying inactivation in *Agrp* gene exhibit significant improvements in reproduction, including normal timing of vaginal opening and estrous cycling, as well as recovery in fertility.[187] In another study, NPY/AgRP neurons were ablated in *ob/ob* mice.[188] The authors reported a restoration in body weight, food intake and glucose tolerance to levels similar to wild-type mice. Interestingly, this manipulation recovered the fertility of either male or female *ob/ob*, indicating that under low leptin levels NPY/AgRP neurons exert an important inhibitory effect on reproductive axis.[188] Leptin probably acts on POMC/CART neurons to regulate reproduction as well. α-MSH is able to activate 70% of GnRH neurons, whereas approximately 15% of GnRH neurons are excited by CART.[189] Additionally, the combined inactivation of LepR and insulin receptor in POMC cells reduces the fertility in mice, elevates serum testosterone levels and causes ovarian abnormalities.[190] Therefore, the current evidence in the literature indicates that LepR-expressing neurons in the MPO, PMv and ARH (NPY/AgRP and POMC/CART cells) are able to sense leptin levels to modulate the onset of puberty and reproduction.

Locomotor activity, neuronal plasticity, development and other brain functions

The biologic effects of leptin extend beyond the regulation of energy balance and glucose homeostasis. There is plenty of information indicating that several behaviors and brain functions are regulated by leptin signaling. Voluntary locomotor activity is directly regulated by leptin signaling, independently of body weight changes. For example, *ob/ob* or LepR-deficient mice show reduced locomotor activity, which is not caused by their morbid obesity. Leptin signaling only in the ARH or specifically in POMC neurons can partially rescue the hypoactivity displayed by LepR-deficient mice.[64,110,166] NPY/AgRP neurons also regulate locomotor activity since LepR ablation only in these cells causes decreased ambulatory activity compared with wild-type mice.[82] Acute activation of MPO LepR-expressing neurons causes

suppression in locomotor activity.[98] However, the reduction in body temperature caused by the activation of MPO LepR neurons could impair locomotion.[98] Mice carrying LepR ablation in LHA neurotensin neurons exhibit decreased locomotor activity as well.[95] These animals show an altered regulation of orexin neurons and mesolimbic dopamine system, since they have lower fasting-induced activation of orexin neurons and reduced orexin expression in the LHA, as well as a blunted amphetamine-induced increase in locomotor activity.[95] As previously mentioned, leptin can directly regulate mesolimbic dopamine system through LepR-expressing cells in the VTA.[100] Knockdown of LepR in the VTA increases locomotor activity of rats.[99] In another study, LepR was selectively inactivated in dopamine neurons.[191] These mice display anxiogenic-like behavior in the elevated plus-maze, light-dark box, social interaction and novelty suppressed feeding tests. However, depression-related behaviors were not affected by the lack of leptin signaling in dopamine neurons.[191] Therefore, several leptin responsive neural populations are responsible to mediate leptin's effects on locomotor activity, including neurons in the ARH, MPO, LHA and VTA. In addition, the direct (through VTA) or indirect (through LHA) regulation of mesolimbic dopamine system allows leptin to control different behaviors, such as anxiety and preference to palatable foods.

Neuroplasticity is the process through which neural circuits adapt to variations in stimuli coming from the environment. Leptin-deficient mice have reduced brain mass and cortical brain volume,[192] and they have an immature expression pattern of synaptic and glial proteins. Some of these defects cannot be reverted by leptin treatment at adulthood.[193] However, leptin treatment in adults with missense leptin mutations is able to increase gray matter concentration in the frontal cortex, left inferior parietal lobule and left cerebellum.[194]

As described above, the most studied role of leptin is related to the regulation of body weight and food intake. However, this function does not begin until the first month of life in rodents. It was shown by Mistry and collaborators that leptin administration peripherally or centrally, even in high doses, has no impact in body weight, food intake or fat deposition until the first month of postnatal life.[195] This explains why *ob/ob* and *db/db* mice express their obese phenotype only after that period. Therefore, leptin's role is possibly different in very young mice. Leptin is expressed in the fetus, but its production originates from diverse tissues since adipose tissue is minimal during this stage of development.[196] The majority of leptin-responsive neurons in adult brain are born in the first 2 weeks of embryonic life.[196] Leptin's transport into the brain through the LepRa is finely regulated since embryonic stage,[197] and leptin reaches the brain at a very young age.[198] Between postnatal days 6 and 14 there is a leptin surge, with concentrations significantly higher than the values exhibited in adult life.[199] To understand the physiologic role of this leptin surge, it is important to state that in mice and rats the hypothalamus begins to develop during mid-gestation and continues to develop during the first weeks of postnatal life.[200] The development of the projections from ARH neurons to different hypothalamic nuclei coincides with the postnatal leptin surge, although it occurs at different moments, starting with the DMH (established by postnatal day 6, P6), whereas those to the PVH develop later, by P8–10, and finally the projections to the LHA are established by P16.[85,201] Previous studies by Bouret and colleagues showed that leptin has an important trophic role in the mouse brain during the first weeks of life by regulating axon growth in specific neuronal populations. Consequently, o*b/ob* mice have fewer projections from the ARH to other brain regions, including the PVH. This deficiency could be reversed only when leptin was replaced in the first weeks of life, whereas leptin treatment in adult *ob/ob* mice was unable to restore these projections.[85] However, despite this critical neonatal window for leptin's neurotrophic action, leptin treatment is still able to revert the obese phenotype of adult *ob/ob* mice, indicating that further studies are still necessary to understand the biologic importance of the neurotrophic effect of leptin.[179] There is evidence that leptin also influences synaptic plasticity. *Ob/ob* mice have altered synaptic inputs in NPY/AgRP/GABA and POMC/CART neurons, with marked excitatory inputs on orexigenic neurons, thus stimulating food intake. In contrast to the critical leptin's neonatal window to regulate axon growth, leptin treatment reverses the altered pattern of the synaptic inputs of *ob/ob* mice within hours.[202]

Several studies have also identified a role of leptin in cognitive processes through activation of LepR in

the hippocampus. It has been reported that leptin regulates hippocampal excitability by modulating large-conductance calcium-activated potassium channels.[203] Leptin can reduce hippocampal excitability in an animal model of epilepsy[204] or act as pro-convusant, depending on the target population of hippocampal cells.[205] The hippocampus is required for learning and memory. The long-term potentiation is a form of synaptic plasticity important for learning/memory and this phenomenon is impaired in *db/db* mice.[206] Additionally, leptin deficiency reduces brain myelination.[207] Obese rats also show memory deficits related tasks,[208] indicating a possible role of leptin in the formation of memory and learning. Baseline neurocognitive tests in a child with a mutation in the leptin gene indicated a developmental cognitive age lower than expected by their chronological age. Interestingly, treatment with leptin improved their neurocognitive skills.[209] LepR-deficient mice also show depression-like and anxiolytic behaviors from a young age, as well as psychosis-like behavior, which is present only in adult animals.[210] On the other hand, animals exposed to stress paradigms have a significant decrease in leptin serum levels, and leptin administration into the hippocampus reverted depressive-like behavior in the forced swim test.[211,212] In summary, there is evidence indicating that leptin can affect numerous cognitive processes and behaviors.

The role of leptin in disease

Potential therapeutic effects of leptin administration

Obesity

Leptin replacement in leptin-deficient subjects leads to enormous beneficial effects restoring their energy balance, glucose homeostasis, neuroendocrine and cognitive dysfunctions.[49,50,61,209] Mutations in the leptin gene can also produce a biologically inactive leptin, in which treatment with recombinant human leptin is able to normalize the eating behavior and cause weight loss.[213] However, these mutations are very rare.[214] The potential therapeutic effects of leptin administration to treat obese humans, who do not carry any mutations in the *Lep* gene, were tested in several clinical trials. However, treatment with exogenous leptin resulted in no or only modest effects on body weight,[215-220] including obese individuals after gastric bypass surgery.[221] Additionally, no significant prevention in calorie restriction-induced neuroendocrine adaptations was achieved with leptin administration.[218,222] These results indicate that in obese individuals with already elevated leptin levels, exogenous leptin no further helps in the body weight management. Thus, leptin administration is likely a poor therapy for the obesity treatment. However, the perception of hunger/satiation was significantly improved in leptin-treated patients.[223,224] Some reports also indicate that leptin administration induces a robust weight loss in a small percentage of patients,[215] suggesting that a subgroup of obese individuals could benefit from leptin treatment.

Lipodystrophy

Since leptin is produced by the adipose tissue, any dysfunction in this organ may affect serum leptin levels. Congenital or acquired generalized lipodystrophy (GL) is a condition characterized by abnormal or degenerative adipose tissue, leading to incapacity to accumulate fat in this tissue that is compensated with lipid deposition in other organs, such as the liver and skeletal muscle. GL can cause severe insulin resistance, hyperglycemia, dyslipidemia and hepatic steatosis. Importantly, patients with GL show low circulating leptin levels. The role of GL-induced leptin deficiency was investigated by studies that treated GL patients with leptin. Leptin administration produced profound improvements in all metabolic defects exhibited by GL patients.[225-228] The beneficial effects of leptin therapy were observed not only in congenital GL, but also in HIV-associated lipodystrophy syndrome,[229,230] and in type 1 diabetes mellitus (T1DM) associated with acquired GL.[231] These findings led the US Food & Drug Administration (FDA) to approve in 2014 Myalept® (metreleptin for injection) as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired GL. This was the first official medical approval of leptin treatment.

Diabetes mellitus

As mentioned earlier, leptin deficiency causes severe insulin resistance, frequently associated with hyperglycemia. Leptin replacement therapy reverses the diabetic phenotype of *ob/ob* mice or leptin deficient humans.[50,51,61] Several studies investigated whether leptin treatment produces beneficial effects on type 2 diabetes mellitus (T2DM) patients.[232,233] In a study,

metreleptin administration in patients with T2DM only reduced glycated hemoglobin (HbA_{1c}) marginally, without altering body weight or circulating inflammatory markers.[233] In other report, recombinant methionyl human leptin for 14 d did not produce any significant effects on insulin sensitivity or body weight of obese people with T2DM.[232] Therefore, in accordance with the clinical trials to evaluate the potential efficacy of leptin to treat obesity, the data available indicates that leptin possesses poor anti-diabetic potential when used in hyperleptinemic obese people with T2DM.

In contrast to the minor effects produced in T2DM, leptin therapy in type 1 diabetic non-obese (NOD) mice normalized circulating levels of glucose, HbA_{1c}, free fatty acids, as well as a wide array of hepatic intermediary metabolites.[234] Compared to insulin monotherapy, leptin lowers plasma and tissue lipids, and lipogenic and cholesterologenic transcription factors and enzymes.[234] The anti-diabetic effects of leptin in T1DM depends on the CNS, since intracerebroventricular infusion of leptin has the same beneficial effects than systemic treatment.[235] The mechanisms of action recruited by leptin to produce such dramatic effects resolving the metabolic dysfunctions in T1DM have been investigated. LepR expression in POMC cells or in GABA-positive neurons is sufficient to mediate the lifesaving and antidiabetic actions of leptin in insulin deficiency.[236] Additionally, leptin administration improves hyperglucagonemia,[234-236] which is a key feature that can lead to hyperglycemia and further complications of T1DM.[237-240] Thus, pre-clinical studies in animal models highlight a promising therapeutic potential of leptin to treat T1DM. Regarding T2DM, leptin therapy produces small effects, possibly because of the already elevated serum leptin levels presented by the majority of type 2 diabetic individuals.

Hypothalamic amenorrhea

The reduction in leptin levels during calorie-restricted conditions is a determining factor that leads to suppression of the reproductive axis.[55,57] Chronic energy deficiency secondary to strenuous exercise and/or decreased food intake can produce functional hypothalamic amenorrhea, which is a condition characterized by the disruption of GnRH secretion and consequently anovulation and infertility. Therefore, under these conditions, hypothalamic amenorrhea may be caused by the relative leptin deficiency produced by chronic negative energy balance. In an elegant study, eight women with hypothalamic amenorrhea due to strenuous exercise or low body weight received recombinant human leptin for up to 3 months.[172] The authors observed that leptin treatment increased mean LH levels and LH pulse frequency after 2 weeks and increased maximal follicular diameter, the number of dominant follicles, ovarian volume and estradiol levels over a period of 3 months. Remarkably, three patients had an ovulatory menstrual cycle and two others had preovulatory follicular development and withdrawal bleeding during treatment.[172] Besides improvements in the reproductive axis,[172,241] leptin treatment in patients with hypothalamic amenorrhea improved bone mineral density and content, as well as markers of bone metabolism suggestive of bone formation.[241,242] Although larger clinical trial studies are still required to better assess the effects of leptin in the hypothalamic amenorrhea, these preliminary findings indicate that leptin treatment may be helpful to improve fertility and bone mineral density in lean hypoleptinemic women.

Leptin resistance and obesity

Definition

As previously mentioned, the high leptin levels and the decreased responsiveness to leptin led the scientific community to hypothesize that obesity is characterized by a condition of leptin resistance. It is worth mentioning that it is believed that leptin triggers more robust biologic responses when its levels decrease, such as during caloric restriction. Therefore, the reduction of leptin levels is a powerful cue to coordinate responses to save energy and increase hunger to increase survival and protect animals from food deprivation. On the other hand, nutrient excess is considered such a rare situation in nature that probably precluded evolution to select mechanisms capable of preventing efficient weight gain. A reduced capacity to respond to chronic high leptin levels is an example of this concept. However, experimental evidence points out possible mechanisms that explain the lower responsiveness to high leptin levels,[44] as described in more details in the following section and summarized in Fig. 6.

Leptin sensitivity in experimental models is normally evaluated by measuring the acute or chronic capacity of exogenous leptin infusion to reduce body weight, adiposity and/or food intake. Leptin sensitivity is also determined by measuring the activation of signaling pathways recruited by LepR after leptin administration (Fig. 2). Using the anorexigenic effects of leptin as readout to determine leptin sensitivity, numerous studies observed that DIO animals showed an attenuated response to leptin.[243] However, a recent study questioned the current view of the importance of leptin resistance to induce obesity.[244] In this study, LepR antagonist administration surprisingly increased feeding and body weight in both lean and DIO mice. As expected, this antagonist had no effect on leptin or LepR-deficient mice.[244] Therefore, although several studies have demonstrated that obesity reduces the anorexigenic effects of leptin, DIO animals still retain some capacity to respond to LepR antagonist.

Regarding the assessment of leptin signaling pathways, Münzberg et al.[45] made a very nice observation indicating that some brain regions are more prone to develop leptin resistance compared with others. In this study, an acute peripheral (intraperitoneal) leptin infusion was able to induce an equivalent number of cells expressing pSTAT3 in the VMH, DMH, PMv and NTS of HFD-induced obese mice, compared with lean animals on normal chow diet.[45] However, the number of pSTAT3-positive cells in the ARH of obese mice was significantly lower compared with lean animals indicating a nucleus-specific leptin resistance.[45] Other studies confirmed these findings[114] and further indicated that NPY/AgRP neurons are first affected by DIO (2 d on HFD are enough to cause leptin resistance in these cells), whereas leptin resistance in POMC neurons requires a longer exposition to HFD.[245] The reason for this selective leptin resistance may be caused by the anatomic position of LepR-expressing cells in relation to the BBB. NPY/AgRP neurons are very near to median eminence, which is a circumventricular organ. Therefore, median eminence presents extensive vasculature and lack of a normal BBB. Consequently, factors in the systemic circulation can affect more significantly neurons located close to this structure than cells of other brain regions. Therefore, ARH cells, especially NPY/AgRP neurons, are robustly affected by the pro-inflammatory and hyperleptinemic effects induced by HFD consumption.[245] Besides HFD consumption, leptin resistance is also observed in other situations, such as pregnancy.[104,246-249] As the primary cause of leptin resistance in pregnancy likely differs from what is observed in DIO, the brain nuclei exhibiting leptin resistance in pregnant animals may also be different. In fact, several studies have observed a lower responsiveness to leptin in the VMH of pregnant animals.[247-250]

The selective leptin resistance may help to explain some metabolic consequences of obesity. While the ability of leptin to regulate the energy balance, body weight and glucose homeostasis is impaired in DIO animals, since ARH is a major area that regulates these functions, others effects of leptin may be upregulated. That seems to be the case of leptin-induced activation of sympathetic nervous system.[114,160,164] As obese animals have high leptin levels and brain nuclei that drive

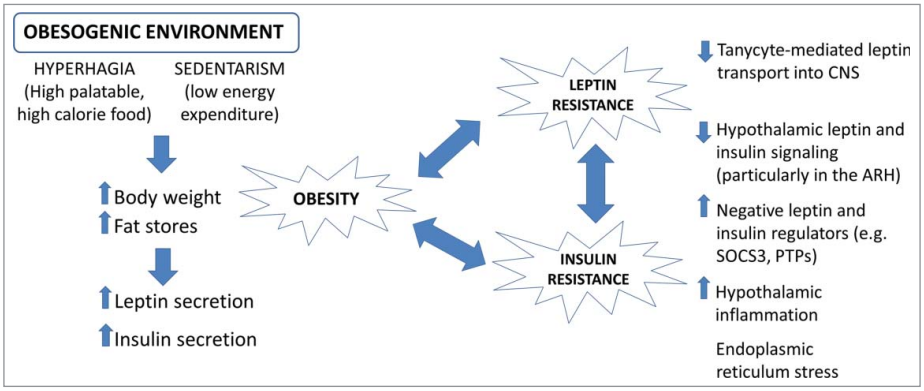

Figure 6. Environmental influences on the development of obesity. Scheme summarizing the mechanisms through which an altered environment can promote obesity and type 2 diabetes mellitus.

leptin-induced activation of sympathetic nervous system maintain leptin sensitivity (e.g., DMH), the overactivation of leptin signaling can, for example, predispose obese individuals to hypertension.[160] Thus, leptin resistance is a complex phenomenon that probably affects some neuronal populations and leptin's functions, but not others.

Mechanisms

Some authors have suggested that leptin resistance may be caused by a limited capacity of leptin to enter into the CNS and therefore activate its cognate receptor in different brain areas. This hypothesis is supported by the fact that leptin enters into the CNS through a saturated transport system,[251] as well as because the cerebrospinal-fluid/serum leptin ratio is decreased in obesity.[252,253] Additionally, some studies have demonstrated that central leptin infusions are more efficient in inducing leptin's anorexigenic effects in obese animals in comparison with peripheral injections, suggesting that leptin transport from systemic circulation to the CNS could represent a limiting factor.[60,243] Some pieces of evidence indicate the participation of short forms of LepR, such as the ObRa, in the leptin transport from systemic circulation to the CNS. For example, rats carrying a mutation that prevents the synthesis of short forms of LepR show decreased transport of leptin across the BBB and develop obesity.[18,254] In addition, the short form of LepR is abundantly expressed in brain microvessels and choroid plexus, and ObRa is able to mediate a transcellular transport of leptin.[39,255] However, other reports presented evidence that leptin transport across the BBB is not mediated by leptin receptors.[256] In another study, mice carrying a mutation that prevents the synthesis of the ObRa isoform were studied.[257] Although these mutants exhibited a reduced cerebrospinal-fluid/serum leptin ratio, they presented very modest metabolic abnormalities suggesting that ObRa only plays a minor role in mediating leptin's effects.[257] More recently, the participation of median eminence tanycytes was described in the leptin transport to the brain.[258] Circulating leptin activates ERK signaling pathway in median eminence tanycytes, which allows leptin passage to the cerebrospinal fluid. Interestingly, leptin taken up by tanycytes accumulates in the median eminence of DIO or *db*/*db* mice, failing to reach the mediobasal hypothalamus.[258] Therefore, although it is not totally clear the exact role of BBB leptin transport as the primary cause of leptin resistance in DIO, defects in this mechanism seem to exert a significant role.

Some authors also suggest that leptin resistance may emerge as a secondary defect caused by the high leptin levels observed in obesity.[259] However, studies that artificially produced high leptin levels chronically observed that animals did not defend a higher body weight, even after cessation of leptin administration, suggesting that hyperleptinemia *per se* does not produce long-term defects to maintain the energy balance and body weight.[60,260] On the other hand, the most robust evidence to explain leptin resistance came from studies that identified intracellular proteins that are able to block the activation of leptin signaling cascades. STAT transcription factors robustly regulate the transcription of genes from the SOCS family, which includes eight intracellular proteins, named as SOCS1 to SOCS7, and CIS. These proteins have a C-terminal motif referred to as the SOCS box and a SH2 domain that allows them to bind to other proteins that contain phosphorylated tyrosine residues.[261] Therefore, SOCS proteins bind to tyrosine phosphorylated proteins leading them to proteasomal degradation or blocking their capacity to transduce intracellular effects.[261] Regarding leptin signaling that conveys its cellular effects through tyrosine phosphorylation and recruits LepR/JAK2/STAT3 pathway, previous studies have identified SOCS3 as the major protein from the SOCS family that is able to inhibit leptin signaling.[262] SOCS3 binds to phosphorylated JAK2 and tyrosine residue 985 of LepR, in both cases blocking the capacity of LepR/JAK2 pathway to transmit its intracellular signal (e.g., to recruit downstream proteins such as STAT3).[263,264] Interestingly, the activation of LepR/JAK2/STAT3 signaling pathway induces a robust SOCS3 expression, indicating that SOCS3 acts as a negative feedback mechanism to modulate leptin signaling (Fig. 1).[262] That is the reason why hyperleptinemic conditions, like obesity, are normally associated with high hypothalamic SOCS3 expression.[262] Therefore, the increased SOCS3 levels in LepR-expressing cells could be a potential cause of leptin resistance in obesity. The important role of SOCS3 controlling leptin sensitivity was confirmed by studies that induced selective SOCS3 inactivation[72,165,167,173,249,250,264-269] or super-expression.[270] For example, brain-specific SOCS3 inactivation increases leptin sensitivity and partially protects

against DIO.[268] SOCS3 expression in specific neuronal populations including POMC,[265] SF1,[167], AgRP[245] and LepR-expressing[165,173,249,250] cells regulates leptin sensitivity and consequently the metabolism. Since SOCS3 also inhibits insulin signaling, and insulin and leptin act together in the CNS to control glucose homeostasis,[271] conditional SOCS3 ablation normally produces beneficial effects on glucose control, especially in obese insulin-resistant animals.[165,265,268]

The SOCS3 capacity to affect leptin signaling and consequently the metabolism is not limited to conditions that simulate pathological states, such as DIO. Recent findings have shown that SOCS3 levels in LepR-expressing cells coordinate the typical metabolic adaptions of pregnancy.[249,250] Pregnant animals must increase their food intake, adiposity and develop a certain level of insulin resistance to properly provide nutrients for the developing fetuses, and later for lactation. During pregnancy, changes in hormone levels (e.g., increased prolactin or placental lactogens levels) induce leptin resistance and may increase hypothalamic SOCS3 levels.[272-274] Selective inactivation of SOCS3 in LepR-expressing cells prevents leptin resistance and thereby attenuates the increased food intake, adiposity and insulin resistance observed in pregnant mice.[249,250] In another study, inactivation of SOCS3 in LepR-expressing cells mitigated post-restriction hyperphagia and weight regain in lean mice by reducing the mRNA levels of hypothalamic orexigenic neuropeptides during fasting.[72]

Another important group of proteins that regulates leptin sensitivity is composed by protein tyrosine phosphatases (PTPs), which catalyze the dephosphorylation of tyrosine residues. Consequently, these proteins can block leptin signaling through the dephosphorylation of LepR, JAK2 or STAT3.[275] The protein tyrosine phosphatase 1B (PTP1B; encoded by *Ptpn1* gene), T-cell protein tyrosine phosphatase (TCPTP; encoded by *Ptpn2* gene) and protein tyrosine phosphatase epsilon (RPTPε; encoded by *Ptpre* gene) produce these effects, regulating negatively LepR signaling. Several studies have demonstrated that hypothalamic expression of PTPs is increased in obese animals and selective ablation of these proteins improves leptin sensitivity and partially prevents HFD-induced obesity and insulin resistance.[46,131,266,276-280]

Leptin signaling can also be positively regulated by adaptor proteins and other enzymes. For example, inactivation of the Shp2 decreases leptin sensitivity and predisposes animals to obesity.[281,282] The cytoplasmic adaptor protein SH2B1 increases leptin sensitivity by binding to phospho-Tyr813 of JAK2 which enhances its activity and the activation of downstream leptin-signaling pathways.[283] SH2B1 can also bind directly to insulin receptor substrate 1 and 2 (IRS1/IRS2), stimulating leptin-induced activation of PI3K signaling pathway.[283] In accordance with these effects, neuron-specific SH2B1 knockout mice exhibit leptin resistance, obesity and hyperglycemia.[284] In summary, several intracellular proteins are able to affect either positively or negatively leptin signaling, representing potential candidates to mediate the leptin resistance observed in specific conditions, such as DIO or pregnancy.

Link between environment and obesity

The increasing prevalence of obesity and other metabolic diseases provides a link between the environmental changes that have occurred in the last decades with an impaired capacity to properly regulate the energy balance (Fig. 6). Regarding this, a frequent consumption of high-palatable/high-caloric diets, associated with a sedentary and stressful lifestyle, somehow disturb the functioning of neurocircuits responsible to control the food intake, body weight and blood glucose levels. The intake of high-palatable/high-caloric diets can disrupt the energy balance via several mechanisms.[285,286] For example, HFD activates proinflammatory responses in the hypothalamus, which disturb the energy and glucose homeostasis.[287] HFD can also lead to suppressed neurogenesis and apoptosis of hypothalamic neurons, especially those that induce satiety.[288,289] The proinflammatory and proapoptotic effects of HFD may involve the activation of toll-like receptor 4 (TLR4), since TLR4 is activated by saturated fatty acids.[290] Consequently, HFD induces the activation of IKKβ/NF-kappaB signaling pathways in the hypothalamus, which induce the production of proinflammatory cytokines, such as TNF-α.[291,292] A high calorie/fat diet can also lead to endoplasmic reticulum (ER) stress.[290,291,293] ER stress is caused by the accumulation of misfolded proteins, which activates the unfolded protein response.[286] This condition, commonly caused by HFD consumption, plays a central role in the development of leptin resistance.[291,294-297]

More recently, several studies described the participation of the gut microbiota in the predisposition to obesity and metabolic complications.[285,298-303] Differences in our diet can change our gut microbiota, impacting in the risk to develop obesity.[300] The gut microbiota can provide short-chain fatty acids or other nutrients after bacterial fermentation, and modulates gastrointestinal permeability and thereby the penetration of bacteria or bacterial products, such as LPS, which can induce intestinal or systemic inflammation.[285,298,301] Interestingly, non-caloric artificial sweeteners or dietary emulsifiers, widely used food additives, can change our gut microbiota and promote metabolic syndrome.[302,303]

Can leptin resistance be treated?

Since leptin resistance is a key feature that predisposes to obesity, the discovery of any treatment capable of preventing or restoring this condition would have a tremendous potential as anti-obesity therapy. Unfortunately, so far there is no efficient method to reestablish leptin sensitivity in obese animals. However, numerous studies have been focused in seeking for potential therapies that can increase leptin sensitivity. Obvious candidates would be compounds that inhibit proteins capable of inducing leptin resistance. Many natural products contain several lignans and flavonoids that exhibit a significant capacity to inhibit PTP1B.[304,305] Resveratrol activates SIRT1, a NAD^+-dependent protein deacetylase, which modulates leptin and insulin sensitivity.[306] Using drug-screening methods, some studies found leptin sensitizer compounds with powerful anti-obesity properties, including the Celastrol, a pentacyclic triterpene, or Withaferin A, a steroidal lactone.[307,308] Amylin is a hormone co-secreted with insulin from pancreatic β-cells, which binds specific receptors in the hindbrain. Interestingly, concurrent peripheral administration of amylin and leptin elicits synergistic anorexigenic effects in DIO animals, indicating that amylin agonists restore leptin responsiveness in DIO.[309-312] Other studies also observed restoration of leptin responsiveness in DIO mice using an optimized leptin analog in combination with exendin-4, a long-acting GLP-1 receptor agonist, or fibroblast growth factor 21.[313]

Not all fatty acids are pro-inflammatory. Actually, unsaturated fatty acids can revert diet-induced hypothalamic inflammation,[314] suggesting that dietary changes prioritizing the intake of unsaturated fatty acids instead of saturated fatty acids can prevent hypothalamic dysfunctions, leptin resistance and consequently obesity. ω-3 polyunsaturated fatty acids activate the G protein-coupled receptor 120 (GPR120) and produce potent anti-inflammatory and insulin-sensitizing effects.[315] Notably, GPR120-deficient mice are prone to develop obesity and GPR120 mutations increase the obesity risk in European populations.[316] ω-3 polyunsaturated fatty acids may also promote neurogenesis in POMC-expressing cells of the ARH, indicating the potential of ω-3 polyunsaturated fatty acids to correct obesity-associated hypothalamic neuronal loss.[317] Regarding non-pharmacological and non-dietary anti-obesity strategies, physical exercise has a great potential. The beneficial effects of exercise for the energy and glucose homeostasis are well-established. However, much less is known about the molecular mechanisms that makes physical exercise an efficient anti-obesity therapy. Previous studies have shown that both endurance,[318,319] and voluntary[320-322] exercise improves leptin sensitivity in peripheral tissues or in the hypothalamus of obese animals. Additionally, acute exercise suppresses hypothalamic PTP1B protein levels, leading to a higher activation of insulin and leptin signaling pathways in obese rats.[323]

Leptin and metabolic programming

Together with the genetic background and the environment where an organism develops, the interaction between mother and fetus during gestation permanently influences the organism's metabolism in adult life, a concept known as metabolic programming.[324] Hales and Baker defined the "thrifty phenotype hypothesis," which suggests that poor nutrition during gestation can permanently program the fetus to develop metabolic disorders such as metabolic syndrome and type 2 diabetes mellitus.[325] The consequences of poor nutrition during gestation for the development of obesity were first observed during the Dutch famine of 1944–1945, where exposition to undernutrition during the first half of pregnancy resulted in high obesity rates, whereas exposition during the last trimester or first months after birth resulted in lower obesity rates.[326] Therefore, depending on the moment where the exposure to

undernutrition occurs, the progeny will be programmed to a higher or lower body mass index.[53]

A recent study using a mouse model of undernutrition during gestation showed that if food is available during the postnatal period, the undernourished offspring often displays accelerated catch-up growth. This fast recovery seems to be mediated by leptin.[327] As mentioned earlier, leptin inhibits NPY/AgRP/GABA neurons in adult animals. However, there is evidence that leptin can activate NPY/AgRP/GABA neurons from postnatal days 13–15 (P13–P15). This opposite effect occurs because of the lack of functional ATP dependent potassium channels in LepR cells at that age. At P21, when pups feed independently, leptin induces depolarization in 41% of the cells, while 25% of neurons are hyperpolarized by leptin. By the fourth week of life, the NPY/AgRP/GABA circuit acquires the adult phenotype.[327] In case of undernutrition followed by overnutrition during lactation, the onset of the potassium channels is delayed and instead of inhibiting food intake leptin stimulates it, favoring the accumulation of energy stores until growth and adiposity are similar to controls.[328]

The opposite scenario, overnutrition, also has severe consequences for the metabolism of the offspring. Several studies have shown that overnutrition before, during and shortly after gestation can induce long-term metabolic disorders in the offspring.[329] Female mice fed a HFD during gestation had hyperglycemic pups with higher adiposity.[330] If the HFD was extended to lactation, the offspring developed greater risk of becoming obese,[331] and the α-MSH and AgRP containing fibers were decreased in the hypothalamus.[332] Similarly to what was seen in rodents, children born of obese mothers have higher chances of developing metabolic syndrome.[333] Rats treated with leptin antagonist during development presented leptin resistance in adult life, and when submitted to HFD they had higher chances to gain more weight than control rats. At 8 months, rats that received leptin antagonist during development became hyperleptinemic with higher adiposity.[334]

Human and animal models of retarded intrauterine growth are more susceptible to develop obesity and metabolic syndrome when challenged with HFD in adult life. Leptin levels increase at the end of embryonic development, but are decreased after birth, being lower in babies with retarded intrauterine growth compared with control newborns,[335] indicating that lower leptin during development participates in the metabolic programming. In rats, neonatal leptin treatment reverses the developmental programming induced by undernutrition during gestation, showing that the neonatal period can be influenced by serum leptin levels.[336]

Concluding remarks

Leptin is a master regulator of energy balance and body adiposity. The vast majority of obese individuals present leptin resistance, and recent evidence indicates that our obesogenic environment contributes to this condition. Although leptin administration is a poor therapy to treat obesity, several pathologies, such as lipodystrophy, hypothalamic amenorrhea and T1DM can benefit from leptin treatment. Leptin also has many other important effects throughout life, which includes the regulation of brain development, behaviors, neuroendocrine axes and autonomic nervous system. More than being a hormone that induces weight loss and satiety, leptin coordinates numerous biologic functions to ensure survival, especially during situations of negative energy balance. This myriad of effects depends on the coordinated action of multiple populations of LepR-expressing neurons.

Abbreviations

AgRP	agouti-related protein
ARH	arcuate nucleus of the hypothalamus
BAT	brown adipose tissue
BBB	blood–brain barrier
CART	cocaine and amphetamine regulated transcript
CCK	cholecystokinin
CNS	central nervous system
DIO	diet-induced obesity
DMH	dorsomedial nucleus of the hypothalamus
DMX	dorsal motor nucleus of the vagus
ER	endoplasmic reticulum
ERK	extracellular signal-regulated kinases
GH	growth hormone
GL	generalized lipodystrophy
GLP-1	glucagon-like peptide-1
GnRH	gonadotropin-releasing hormone
GPR120	G protein-coupled receptor 120
HFD	high-fat diet

IL	interleukin
IRS	insulin receptor substrates
JAK	Janus kinase
LepR	leptin receptor
LH	luteinizing hormone
LHA	hypothalamic area
LPS	lipopolysaccharide
MCH	melanin-concentrating hormone
MCR	melanocortin receptors
MPO	median preoptic area
nNOS	neuronal NO synthase
NO	nitric oxide
NOD	non-obese diabetic mice
NPY	neuropeptide Y
NTS	nucleus of the solitary tract
Ob-R	leptin receptor
PBN	parabrachial nucleus
PI3K	phosphatidylinositol 3-kinase
PMv	ventral premammillary nucleus
POMC	proopiomelanocortin
PTP	protein tyrosine phosphatases
PTP1B	protein tyrosine phosphatase 1B
PVH	paraventricular nucleus of the hypothalamus
RPTPε	protein tyrosine phosphatase epsilon
SF1	steroidogenic factor-1
SH2	Src homology 2
Shp2	Src homology 2-containing tyrosine phosphatase
SOCS	suppressor of cytokine signaling
STAT	signal transducer and activator of transcription
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TCPTP	T-cell protein tyrosine phosphatase
TLR4	toll-like receptor 4
TNF	tumor necrosis factor
TRH	thyrotropin-releasing hormone
UCP1	uncoupling protein 1
VMH	ventromedial nucleus of the hypothalamus
VTA	ventral tegmental area
α-MSH	α-melanocyte-stimulating hormone.

Disclosure of potential conflicts of interest

No potential conflicts of interest are disclosed.

Acknowledgments

The authors would like to thank Ana Maria P. Campos for helping to produce the mouse brain photomicrographs.

Funding

This work was supported by the São Paulo Research Foundation (FAPESP; grants number: 2015/10992-6 to J.D. and 2014/11752-6 to A.M.R.L.).

About the authors

Jose Donato Jr., PhD, is an Associate Professor of the Department of Physiology and Biophysics at the University of São Paulo (USP), Brazil. He received his PhD in Morpho-functional Sciences from USP in 2008, followed by a postdoctorate at the University of Texas Southwestern Medical Center, Dallas, TX. Back to Brazil in 2012, Dr. Donato set up his laboratory focused in understanding the importance of hormone signaling in the brain. So far, his group published several papers studying the effects of leptin, prolactin, estradiol and growth hormone on brain functions, especially regarding the regulation of energy balance and glucose homeostasis.

Angela M. Ramos-Lobo, MSc, is a PhD student under Dr. Donato's supervision. She graduated in Biology at the University of Buenos Aires in 2010 and received her MSc in Sciences from USP in 2013. Her PhD focuses on understanding the consequences of the absence of leptin signaling in early life.

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