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Q1 Review Article

2 Control of respiratory and cardiovascular functions by leptin

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A B S T R A C T

Leptin, a peptide hormone produced by adipose tissue, acts in brain centers that control critical physiological Q3 functions such as metabolism, breathing and cardiovascular regulation. The importance of leptin for respiratory 20 control is evident by the fact that leptin deficient mice exhibit impaired ventilatory responses to carbon dioxide 21 (CO₂), which can be corrected by intracerebroventricular leptin replacement therapy. Leptin is also recognized as 22 an important link between obesity and hypertension. Humans and animal models lacking either leptin or func- 23 tional leptin receptors exhibit many characteristics of the metabolic syndrome, including hyperinsulinemia, insu- 24 lin resistance, hyperglycemia, dyslipidemia and visceral adiposity, but do not exhibit increased sympathetic 25 nerve activity (SNA) and have normal to lower blood pressure (BP) compared to lean controls. Even though pre- 26 vious studies have extensively focused on the brain sites and intracellular signaling pathways involved in leptin 27 effects on food intake and energy balance, the mechanisms that mediate the actions of leptin on breathing and 28 cardiovascular function are only beginning to be elucidated. This mini-review summarizes recent advances on 29 the effects of leptin on cardiovascular and respiratory control with emphasis on the neural control of respiratory 30 function and autonomic activity. Q30

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Introduction

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Obesity is a major public health problem worldwide. The genesis of 57 obesity is multifactorial involving genetic, metabolic and environmental 58 aspects. Progress in endocrinology research has shown that the adipo- 59 cyte is an endocrine tissue producing several active substances, such 60

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as interleukin-6, tumor necrosis factors- α , adiponectin and leptin, which modulate many physiological functions. In this review, we focus on the cardiorespiratory actions of leptin.

Leptin circulates freely in the plasma and crosses the blood–brain barrier via a saturable receptor-mediated transport system [69] to enter into the central nervous system centers (CNS) where it regulates neural pathways that control appetite [39], sympathetic nerve activity (SNA) and thermogenesis [63,80]. In addition, it has been suggested that leptin stimulates chemorespiratory responses [5–7,47].

Leptin's effects on cardiovascular and respiratory function are slow in onset, often requiring several hours, or even days, before major changes are observed. Although the precise mechanisms by which leptin modulates several physiological functions are not well understood, the slow onset is consistent with the idea that leptin's actions may involve changes in gene expression and protein synthesis, thus requiring a few days for full effects.

Leptin receptors (LRs) belong to the class of I cytokine receptor superfamily [53,88]. Alternative splicing of the LR gene generates 6 leptin receptor isoforms, termed from Ob-Ra to Ob-Rf, which have an identical extracellular N-terminal. Ob-Re is the only soluble receptor form, probably binding circulating leptin and affecting its stability and availability [34,93]. Four of the remaining 5 isoforms have short C-terminal domains and are considered to be mainly involved in endocytosis and transport of leptin across the blood–brain barrier [3]. The isoform Ob-Rb, however, has a long intracellular domain and is essential for mediating leptin's intracellular signal transduction [89].

Stimulation of LR by leptin activates Janus tyrosine kinases (JAK), especially JAK2 [35]. In the central nervous system (CNS), leptin increases the activity of JAK2 to trigger three major intracellular pathways: 1) phosphorylation of tyrosine (Tyr) residue 1138 to recruit latent signal transducers and activators of transcription 3 (STAT3) to the LR-JAK2 complex, resulting in phosphorylation and nuclear translocation of STAT3 to regulate transcription; 2) insulin receptor substrate (IRS2) phosphorylation which activates phosphatidylinositol 3-kinase (PI3K) which appears to be involved in regulating rapid non-genomic events affecting neuronal activity and neuropeptide release; and 3) Tyr985 phosphorylation which recruits the tyrosine phosphatase (SHP2) to activate ERK (MAPK).

Although the roles of these intracellular signaling pathways in mediating the various actions of leptin are the subject of intense investigation, especially on appetite behavior [28], their importance in SNA and breathing control is only beginning to be elucidated. Strong evidence shows that leptin requires activation of the brain melanocortin system, including activation of proopiomelanocortin (POMC) neurons and melanocortin 4 receptors (MC4R) to exert most of its effects on blood pressure (BP) and ventilatory function [6,7,22,77].

The hypothalamic arcuate nucleus (ARC) was initially considered the main site of leptin actions; however, increasing evidences suggest that leptin acts on a more extensive brain network [39]. For example, functional LRs are present in the nucleus of the solitary tract (NTS) [45,65], an important center involved in cardiorespiratory function. Thus, the focus of this mini-review is on the brain circuits and potential mechanisms that mediate the effects of leptin on respiratory function and cardiovascular regulation.

Leptin and breathing control

Leptin and central chemoreception

Accumulated evidence suggests a role for leptin in control of breathing. Initial studies evaluating the ventilatory responses to CO₂ in leptin-deficient (ob/ob) mice demonstrated impairment of breathing function in these mice [73,87]. This attenuated hypercapnic ventilatory response in ob/ob mice improved after 3 days of systemic leptin administration suggesting an important stimulatory effect of leptin on breathing [73]. In addition, a study performed in anesthetized rats showed that acute

systemic infusion of leptin (for 90 min) elicited a long-lasting increase in the amplitude of phrenic nerve discharge that remained elevated for over 1 h after terminating the leptin infusion [12]. Moreover, the 4th ventricle leptin administration for 3 days also enhanced the ventilatory responses to CO₂, whereas the same dose injected subcutaneous, did not significantly alter central chemoreflex in ob/ob mice [5]. This finding suggests that the facilitation of ventilatory responses to hypercapnia by leptin in ob/ob mice depends on its direct action in the CNS and not due to a peripheral action of leptin resulting from spillover into the systemic circulation.

In order to better understand the CNS mechanisms activated by leptin to modulate chemosensory control of ventilation, the effects of leptin administration into specific medullary brain areas involved with breathing control were investigated. Leptin administration into the NTS, a primary site of peripheral chemorespiratory afferents in the brainstem, of anesthetized rats increased respiratory motor output and ventilatory response to CO₂ potentially via inhibition of the Hering–Breuer reflex [46,47]. It was hypothesized that elevated PaCO₂ reduces the effectiveness of the Hering–Breuer modulation of respiratory pattern facilitating the elimination of CO₂ [68].

Leptin injections into the NTS also attenuate the cardiovagal component of the baroreceptor reflex [1] and potentiate the sympathoexcitatory responses evoked by the activation of the chemoreflex [15]. In addition, systemic administration of leptin increases c-fos expression in neurons of the caudal NTS that express LR [30,39], indicating that leptin may activate NTS neurons involved with the cardiorespiratory reflex.

In addition to its effects in the NTS, leptin may also contribute to the chemoreflex by acting in the ventral surface of the medulla where several nuclei involved in breathing control are located. Leptin receptors are expressed in adrenergic/noradrenergic C1/A1 cells which overlap the rostral ventrolateral medulla (RVLM). Therefore, preautonomic neurons in the RVLM may express leptin receptors which allow cardiovascular effects of leptin by directly increasing the activity of these neurons [4]. Moreover, administration of leptin for 3 consecutive days into the RVLM increased baseline ventilation and ventilatory response to hypercapnia in ob/ob mice [6,7]. Although multiple mechanisms involved in chemoreception at level of the ventral surface of the medulla have been described including modulation of glutamatergic neurons of the retrotrapezoid nuclei (RTN) [42] and purinergic glial cells that release adenosine 5' triphosphate (ATP) in response to CO₂ stimulation [71,92], the mechanisms by which leptin contributes to the chemoreflex is still unclear and remains as an important area for investigation.

Involvement of melanocortin system in mediating leptin's effects on ventilation

Leptin depolarizes POMC neurons leading to the release of α -melanocyte stimulating hormone (α -MSH) which, in turn, activates the MC3/4R located in several hypothalamic nuclei as well as in the brainstem [18,70].

Only few studies have examined the participation of the melanocortin system in mediating the effects of leptin on ventilation. Polotsky et al. [77] investigated the ventilatory responses of obese agouti yellow mice, a model that overexpresses the agouti protein which inhibits MC3/4R. They reported that agouti yellow mice exhibited attenuated ventilatory responses to CO₂ but a normal ventilatory response to hypoxia, suggesting that the melanocortin system may play an important role in mediating the ventilatory responses to hypercapnia.

We found that chronic central MC3/4R antagonism for 6 days reduced the ventilatory response to hypercapnia and abolished leptin's ability to increase baseline ventilation in rats [6,7]. Our data suggest that the effects of leptin on ventilation depend on activation of the brain–melanocortin system. We also demonstrated attenuated ventilatory responses to CO₂ in mice with LR deficiency specifically in POMC neurons, reinforcing the concept that leptin-induced improvement of ventilatory function is mediated by the brain melanocortin system [6,7].

The MC3/4R is expressed in the hypothalamus, including paraventricular hypothalamus (PVN), dorsomedial hypothalamus (DMH) and peri-formical nuclei (PeF) [50]. These nuclei, in addition to mediating metabolic and cardiovascular functions, are involved with breathing modulation under certain conditions, in particular during hypercapnia. The activation of the PVN or DMH produces an activation of phrenic nerve [31,57,59,95]. Additionally, disinhibition of PeF nuclei in the hypothalamus promotes an increase of blood pressure, phrenic nerve discharge and firing rate of the chemosensitive retrotrapezoid neurons in isoflurane-anesthetized rats [31]. The specific effects of leptin and melanocortin system activation in each one of these hypothalamic areas in mediating breathing have, to our knowledge, not been evaluated; however, the involvement of leptin with hypothalamic modulation of respiratory control is possible. This is an area for further investigations.

Besides the CNS action of leptin in modulating ventilation, leptin has an important role in controlling bronchial diameter [2,11,49,83]. The absence of leptin is the main cause of increased airway resistance in obese leptin-deficient (ob/ob) mice and leptin receptor-deficient (db/db) mice [2]. It is important to note that leptin administration in trachea rings evoked no changes in the bronchial diameter [72] whereas intracerebroventricular (i.c.v.) administration of leptin for 5 days decreased airway resistance [2]. These findings suggest that the effects of leptin on airway resistance may also be mediated by leptin's actions on the CNS. Moreover, leptin-induced modulation of respiratory resistance appears to be independent of the brain melanocortin system since mice lacking MC3/4R exhibit normal airway resistance [2].

Leptin and peripheral control of breathing function

In addition to leptin's CNS action to modulate respiratory function, leptin may act on peripheral tissues involved with ventilatory control, including arterial chemoreceptors and lung tissue [17,40,67]. Leptin appears to be secreted by various epithelial tissues including bronchial epithelial cells (BECs) and type II pneumocytes [90]. High levels of LRs have been observed in proximal airway biopsies where leptin is thought to modulate inflammatory response [61,90].

Peripheral chemoreceptors localized predominantly within the carotid bodies also present LR isoform b in type-1 cells [78]. These cells play an integral role in detecting changes in PO₂ by transducing this chemical signal to sensory afferent neurons within the petrosal (PG) and nodose (NG) ganglia to trigger brainstem autonomic reflex pathways [33]. In addition to carotid body glomus cells, LRs are also present in neurons within both the PG and NG [67]. The same study showed that intravenous injections of leptin induce phosphorylation of signal transducer and activator of transcription 3 (pSTAT3), fos and Fra-1 within carotid body cells, similar to the response produced by hypoxia. Taken together, these observations also point toward a potential contribution of leptin in the peripheral chemoreflex response.

Breathing disorders and impairment of leptin function in humans

Increased leptin levels have been reported in obese subject's leading to a state of leptin resistance. In obese patients, high concentrations of serum leptin are associated with reduced respiratory drive and impaired hypercapnic responses in men and women, suggesting resistance to the effects of leptin on respiratory function [9,60,75]. However, hypoxemia stimulates leptin secretion [41], suggesting that leptin resistance and hyperleptinemia might be caused by hypoventilation. In support to this concept, patients with obstructive sleep apnea syndrome (OSAS) who had high levels of leptin presented normal plasma leptin levels after nasal continuous positive airway pressure (NCPAP), suggesting that once the hypoxemia is corrected, leptin levels return to normal [13,76]. Similar results were found in patients with obese hypoventilation syndrome (OHS) using non-invasive ventilation. The reduction of leptin levels after the treatment in this case appears to be independent of any change in body weight [94].

Obesity-induced breathing disorders also lead to cardiovascular complications, including arrhythmias and hypertension. Hypoxia, resulting from obstructive apneic episodes, is a potent stimulator of SNA via a complex reflex mechanism that alters heart rate and BP. During the apneic episode, the combination of hypoxia and the absence of airflow results in carotid body chemoreceptor stimulation, leading to reflex bradycardia via vagal afferents [19,20]. However, in the presence of airflow, in the postapneic ventilation phase, a tachycardia occurs due to inhibition of parasympathetic outflow and unopposed sympathetic outflow to the heart [54]. The long-term effects of OSA are not well understood, although autonomic nervous system dysregulation with chronic sympathetic activation and development of systemic hypertension are usually present.

Leptin may contribute to the development of hypertension caused by hypoxia. As mentioned, hypoxia increases leptin release from adipocytes. Chronic leptin infusion raises BP due to activation of renal sympathetic nerve activity [43]. This effect of hyperleptinemia on BP seems opposite to the resistance to leptin's anorexic and respiratory effects. While the excess of leptin fails to modulate appetite and ventilation, its action on sympathetic activity appears to remain effective.

Leptin and cardiovascular function

Leptin regulates sympathetic outflow and blood pressure

Leptin not only plays a role in the modulation of breathing and regulation of SNA to tissues involved in the breathing process but also modulates SNA to other organs, some of which contribute to the regulation of BP. For instance, acute intravenous or i.c.v. administration of leptin increased SNA to brown adipose tissue, kidneys and adrenal gland in lean rats [29,44]. Acute hyperleptinemia also increases muscle SNA, as assessed by microneurography [58]. Chronic infusions of leptin to produce increases in circulating leptin levels comparable to those found in severe obesity evoked sustained increases in BP that can be completely prevented by α and β adrenergic receptors blockade [10]. Leptin-mediated increases in BP are gradual and occur over several days, indicating a slow-acting mechanism consistent with the modest increases in renal SNA and increased renal tubular sodium reabsorption [84]. Although the chronic hypertensive effects of leptin in lean animals are modest, they are more significant when taking into account the accompanying marked decreases in food intake and weight loss which would normally tend to lower SNA and BP.

A major role for leptin in contributing to increased BP also comes from the studies of Lim and colleagues who showed that increases in BP and renal SNA in obese rabbits fed with a high fat diet were attenuated by acute (90 min) i.c.v. administration of a selective leptin receptor antagonist [56]. Thus, blockade of the actions of endogenous leptin lowers BP in obese animals, further supporting the concept that leptin, at physiological concentrations, can cause chronic increases in BP, at least in experimental animals, and may contribute to obesity induced hypertension. Moreover, mice with leptin deficiency (ob/ob mice) are extremely obese and have many metabolic abnormalities, including insulin resistance, hyperinsulinemia, and dyslipidemia which have been suggested to raise BP. However, mice with leptin deficiency are not hypertensive and tend to have lower BP and reduced SNA compared to lean control mice [24,62]. Similar findings are observed in humans with leptin deficiency who also exhibit early-onset morbid obesity and many characteristics of the metabolic syndrome but these individuals usually are not hypertensive and do not have evidence of increased SNA [74]. In fact, humans with leptin gene mutation show postural hypotension and attenuated renin–angiotensin–aldosterone system responses to upright posture [74]. Collectively, these observations support a role for leptin as a link between obesity, increased SNA and elevated BP.

The effects of leptin to increase SNA and BP however, are partially counterbalanced by metabolic actions of leptin. For example, leptin

decreases appetite and increases energy expenditure which tend to reduce adiposity and cause rapid weight loss, at least in lean subjects who are sensitive to the metabolic effects of leptin. These effects would tend to reduce BP. In addition, leptin also stimulates endothelial-derived nitric oxide (NO) formation, at least in subjects with normal endothelial function. Frühbeck [32] showed, for example, that acute infusion of leptin increased serum NO concentrations and after the inhibition of NO synthesis leptin significantly raised BP. After SNA blockade, however, acute leptin infusion reduced BP [32]. Blockade of NO synthesis also greatly exacerbated the chronic effects of leptin to raise BP and heart rate (HR) [52]. Thus, to the extent that obesity causes endothelial dysfunction and impaired NO formation, one might expect greater leptin-mediated increases in BP than in lean subjects, especially if obesity does not induce resistance to the SNA responses to leptin. Moreover, if obesity is associated with resistance to the anorexic effects of leptin with preserved effects on SNA, as previous suggested [64], this would amplify the hypertensive effects of leptin since the effects of leptin to cause weight loss and associated decreases in BP might be attenuated.

Leptin acts in different brain regions to regulate SNS activity and blood pressure

High levels of leptin receptor mRNA and protein are expressed in the forebrain, especially in the ventromedial hypothalamus, arcuate nucleus (ARC) and dorsomedial areas of the hypothalamus, as well as in vasomotor centers of the brainstem [30,64]. Although the brain centers that mediate leptin's action on SNA and BP have not been precisely mapped, hypothalamic centers as well as certain extra-hypothalamic regions (e.g. brainstem, subfornical organ – SFO) appear to be important in mediating the effects of leptin on SNA and BP [64]. Acute microinjections of leptin into the ARC increase SNA to the kidneys and to brown adipose tissue (BAT) [79], while site specific ARC deletion of LR markedly attenuates the rise in renal and BAT SNA evoked by leptin, suggesting that the ARC is an important site for leptin-mediated modulation of SNSA to several tissues [79]. In fact, deletion of leptin receptors only in POMC neurons, which comprise an important portion of the neuronal types within the ARC, prevents the rise in BP evoked by chronic hyperleptinemia [25,26]. Other nuclei in the hypothalamus have also been implicated in the effects of leptin on SNA. The ventromedial and dorsomedial hypothalamus, for example, appear to contribute to leptin-mediated increases in SNA to the kidneys, skeletal muscle and BAT [64].

Extra-hypothalamic regions may also play a role in mediating leptin's effect on SNA. Microinjection of leptin into the NTS in the brainstem increases renal SNA and acutely raised BP [63]. Additionally, intracarotid injection of leptin excited presympathetic neurons of the RVLM increasing the renal SNA, suggesting that leptin has a direct action on ventral centers of the medulla [97]. Young et al. [96] showed that mice with specific deletion of LR in SFO neurons had normal BAT SNA responses to systemic or i.c.v. administration of leptin but did not exhibit the expected increase in renal SNA. Collectively, these studies suggest that leptin may act on several brain regions in concert to regulate SNA.

Intracellular signaling and specific CNS areas that may mediate differential control of cardiovascular and metabolic functions by leptin

Deletion of STAT3 specifically in POMC neurons attenuated leptin's ability to raise BP but had only minor effects on leptin's actions on food intake and energy expenditure [28,36]. Pharmacological blockade of PI3K abolished the acute effects of leptin to increase renal SNA, which suggests that the IRS2–PI3K pathway may also contribute to leptin's effect on SNA and BP [81]. To our knowledge, however, no long-term studies have tested whether chronic blockade of the IRS2–PI3K pathway abolishes or attenuates the long-term effects of sustained hyperleptinemia to increase SNA and BP. Deletion of IRS2 in the entire CNS causes only moderate obesity and slight hyperphagia associated

with normal anorexic and weight loss responses to leptin [8,14]. These observations suggest that IRS2–PI3K signaling contributes modestly to body weight regulation but may mediate, at least in part, the action of leptin on SNA.

The SHP2–MAPK pathway has been shown to participate in energy balance and metabolism as neuronal deletion of SHP2 causes obesity associated with hyperphagia and diabetes [51]. Chronic effects of hyperleptinemia to increase BP were attenuated in mice with forebrain deletion of SHP2 [27] suggesting that SHP2 signaling may also be important in mediating the effects of leptin on SNA and BP. Further studies are needed, however, to assess the role of these pathways in mediating the chronic effects of leptin on SNA and BP in obesity.

Role of the CNS melanocortin system in mediating the effects of leptin on SNA and BP regulation

Although the precise intracellular events and brain regions by which leptin regulates body weight homeostasis and cardiovascular function are not completely understood, strong evidence suggests that leptin requires activation of the brain melanocortin system, including activation of POMC neurons and MC4R, to exert most of its effects on renal SNA and BP regulation [22,86]. Activation of LR in POMC neurons is critical for leptin's ability to increase SNA and BP [25,26], while activation of MC4R using synthetic agonists increases renal SNA, BP and HR in experimental animal models as well as in humans ([22,37,48]; Sayk et al., 2010). Furthermore, mice with whole body MC4R deficiency not only are hyperphagic, obese, and have many characteristics of metabolic syndrome including hyperglycemia, hyperinsulinemia, visceral adiposity and dyslipidemia despite markedly elevated blood leptin levels, but also are completely unresponsive to the effects of leptin to increase renal SNA and BP [82,86]. In addition, mutations in POMC or MC4R genes lead to severe early-onset obesity and dysregulation of appetite in humans who, despite pronounced obesity, exhibit reduced BP, HR and 24-h urinary catecholamine excretion, lower prevalence of hypertension, and reduced SNA in response to acute stress [37,38]. Taken together, these studies strongly suggest that a functional MC4R is necessary for obesity and hyperleptinemia to increase SNA and cause hypertension. Although previous studies suggested that MC4R in the PVN and preganglionic sympathetic neurons in the brainstem modulate SNA and BP [55,85], additional long-term studies are needed to examine the brain regions where MC4R regulate SNA and cardiovascular function.

Perspectives and conclusion

In this review we highlight recent advances on leptin's role in cardiorespiratory physiology. Leptin has emerged as a multifunctional peptide able to not only regulate energy balance, but also modulate cardiovascular and respiratory functions. Although the precise mechanisms by which leptin exerts its effects on respiratory and cardiovascular functions are still under investigation, strong evidence suggests an important involvement of the CNS and the brain melanocortin system.

Leptin has a stimulatory effect on ventilatory response to CO₂ and these responses are likely mediated by leptin's action in hypothalamic and brainstem nuclei (Fig. 1). In the hypothalamus, leptin's effect on ventilation appears to be mediated by the melanocortin system. However, the role of the melanocortin system in contributing to the brainstem (e.g. NTS and rostral ventrolateral medulla) actions of leptin on ventilatory function has not been investigated.

In addition to its effects on respiratory function, leptin also plays an important role on cardiovascular regulation and is an important link between excess weight gain and increased SNA and hypertension. Although the precise mechanisms by which leptin regulates SNA and BP are still unclear and represent an area of intense investigation, strong evidence suggests a critical role of the brain melanocortin system and the activation of LR in various areas of the CNS including the forebrain

Fig. 1. Schematic representation of the hypothesized brain site where leptin regulates appetite, energy expenditure, blood pressure and breathing. Hypothalamus: (ARC) arcuate nucleus, (PVN) paraventricular nucleus and (LH) lateral hypothalamus. Brainstem: (LC) locus coeruleus, (PBN) parabrachial nuclei, (KF) Kölliker Fuse, (NTS) nucleus of the solitary tract, (DMV) dorsal motor nucleus vagus, (7N) facial nucleus, (NA) ambiguous nuclei, (RTN) retrotrapezoid nuclei, (RVL) rostral ventrolateral nuclei, (BötC) Böttinger nuclei, (preBötC) pre-Böttinger complex and (VRG) ventral respiratory group. RSNA, renal sympathetic nerve activity; POMC, proopiomelanocortin neurons; α-MSH, α-melanocyte stimulating hormone and MC4R, melanocortin 4 receptor.

(e.g. hypothalamus) as well as the brainstem centers (Fig. 1). Therefore, future investigations are needed to unravel the areas of the brain and signaling pathways by which the leptin–melanocortin system affects respiratory and cardiovascular functions.

Conflict of interest

We have no conflict of interest to disclose.

Q26 Uncited references

[16,21,23,66,91]

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