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Minireview

Control of respiratory and cardiovascular functions by leptin

M. Bassi [a,*], I.F. Werner [a], D.B. Zoccal [a], J.V. Menani [a], E. Colombari [a], J.E. Hall [b], A.A. da Silva [b], J.M. do Carmo [b], D.S.A. Colombari [a]

[a] Department of Physiology and Pathology, School of Dentistry, São Paulo State University (UNESP), Araraquara, SP, Brazil
[b] Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

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ABSTRACT

Leptin, a peptide hormone produced by adipose tissue, acts in brain centers that control critical physiological functions including metabolism, breathing and cardiovascular function. The importance of leptin for respiratory control is evident by the fact that leptin deficient mice exhibit impaired ventilatory responses to carbon oxide (CO_2), which can be corrected by intracerebroventricular leptin replacement therapy. Leptin is also recognized as an important link between obesity and hypertension. Humans and animal models lacking either leptin or functional leptin receptors exhibit many characteristics of the metabolic syndrome, including hyperinsulinemia, insulin resistance, hyperglycemia, dyslipidemia and visceral adiposity, but do not exhibit increased sympathetic nerve activity (SNA) and have normal to lower blood pressure (BP) compared to lean controls. Even though previous studies have extensively focused on the brain sites and intracellular signaling pathways involved in leptin effects on food intake and energy balance, the mechanisms that mediate the actions of leptin on breathing and cardiovascular function are only beginning to be elucidated. This mini-review summarizes recent advances on the effects of leptin on cardiovascular and respiratory control with emphasis on the neural control of respiratory function and autonomic activity.

Contents

Introduction

Obesity is a major public health problem worldwide. The genesis of obesity is multifactorial involving genetic, metabolic and environmental aspects. Progress in endocrinology research shows that the adipocyte

* Corresponding author at: Department of Physiology and Pathology, School of Dentistry of Araraquara, São Paulo State University, 1680 Humaitá St., Araraquara, São Paulo CEP: 14801-903, Brazil.
E-mail address: mbassi@foar.unesp.br (M. Bassi).

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is an endocrine tissue producing several active substances, such 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 [64] to enter central nervous system centers (CNSs) where it regulates neural pathways that control appetite [37], sympathetic nerve activity (SNA) and thermogenesis [58,75]. In addition, previous studies have suggested that leptin stimulates chemorespiratory responses [4,6,45].

Leptin receptors (LRs) belong to the class I cytokine receptor superfamily [50,83]. 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 [32,88]. 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 [84].

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 (Grill 2006). For example, functional LRs are present in the nucleus of the solitary tract (NTS) [43,60], an important center involved in cardiorespiratory function.

Stimulation of LR by leptin activates janus tyrosine kinases (JAK), especially JAK2 [33]. 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 the 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 [27], 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 [5,21,72]. 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 CO_2 in leptin-deficient (ob/ob) mice demonstrated impairment of breathing function in these mice [68,82]. This attenuated hypercapnic ventilatory response observed in ob/ob mice was improved after 3 days of systemic leptin administration suggesting an important stimulatory effect of leptin on breathing [68]. 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 [11]. Moreover, we demonstrated that 4th ventricle leptin administration for 3 days also enhanced the ventilatory responses to CO_2 indicating that the central action of leptin facilitates the central chemoreflex [4].

In order to better understand the CNS mechanisms activated by leptin that modulate chemosensory control of ventilation, previous studies investigated the effects of leptin administration into specific medullary brain areas involved with breathing control. Leptin administration into the NTS, a primary site of peripheral chemorespiratory afferents of the brainstem of anesthetized rats increased respiratory motor output and ventilatory response to CO_2 potentially via inhibition of the Hering–Breuer reflex [44,45]. It was hypothesized that elevated $PaCO_2$ reduces the effectiveness of the Breuer–Hering modulation of respiratory pattern that facilitates elimination of CO_2 (as described by [63]) and that the stimulatory effect of leptin on chemoreflex responses may depend on a reduction of the effectiveness of Breuer–Hering reflex.

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 [14]. In addition, systemic administration of leptin increases c-fos expression in the neurons of the caudal NTS that express LR [29]; Elmiquist et al., 1998; [37], 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. For instance, administration of leptin for 3 consecutive days into the rostral ventrolateral region of the medulla increased baseline ventilation and hypercapnic ventilatory response in ob/ob mice [5]. 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) [40] and purinergic glial cells that release adenosine 5´-triphosphate (ATP) in response to CO_2 stimulation [66,87], the mechanisms by which leptin contributes to the chemoreflex is still unclear and remains 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 alpha-melanocyte stimulating hormone (α-MSH) which, in turn, activates the MC3/4R located in several hypothalamic nuclei as well as in the brainstem [17,65].

Only a few studies have examined the participation of the melanocortin system in mediating the effects of leptin on ventilation. Polotsky et al. [72] 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 CO_2 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 in rats and abolished leptin's ability to increase baseline ventilation. Our data suggest that the effects of leptin on ventilation depend on the activation of the brain-melanocortin system. We also demonstrated attenuated ventilatory responses to CO_2 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 [5].

Besides the CNS action of leptin in modulating ventilation, leptin has an important role in controlling bronchial diameter [2,10,47,78]. Previous studies showed that the absence of leptin action is the main cause of increased airway resistance present 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 [67] whereas intracerebroventricular (i.c.v.) administration of leptin for 5 days decreased airway resistance

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