Biochimica et Biophysica Acta xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Direct and indirect effects of leptin on adipocyte metabolism ☆

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ARTICLE INFO

Article history:
Received 19 February 2013
Received in revised form 18 April 2013
Accepted 6 May 2013
Available online xxxx

Keywords:
Leptin receptor
Lipolysis
Lipogenesis
Sympathetic nervous system
Insulin

ABSTRACT

Leptin is hypothesized to function as a negative feedback signal in the regulation of energy balance. It is produced primarily by adipose tissue and circulating concentrations correlate with the size of body fat stores. Administration of exogenous leptin to normal weight, leptin responsive animals inhibits food intake and reduces the size of body fat stores whereas mice that are deficient in either leptin or functional leptin receptors are hyperphagic and obese, consistent with a role for leptin in the control of body weight. This review discusses the effect of leptin on adipocyte metabolism. Because adipocytes express leptin receptors there is the potential for leptin to influence adipocyte metabolism directly. Adipocytes also are insulin responsive and receive sympathetic innervation, therefore leptin can also modify adipocyte metabolism indirectly. Studies published to date suggest that direct activation of adipocyte leptin receptors has little effect on cell metabolism in vivo, but that leptin modifies adipocyte sensitivity to insulin to inhibit lipid accumulation. In vivo administration of leptin leads to a suppression of lipogenesis, an increase in triglyceride hydrolysis and an increase in fatty acid and glucose oxidation. Activation of central leptin receptors also contributes to the development of a catabolic state in adipocytes, but this may vary between different fat depots. Leptin reduces the size of white fat depots by inhibiting cell proliferation both through induction of inhibitory circulating factors and by contributing to sympathetic tone which suppresses adipocyte proliferation. This article is part of a Special Issue entitled: Modulation of Adipose Tissue in Health and Disease.

1. Introduction

Early animal and human studies indicated that mechanisms are in place to balance energy intake and energy expenditure over periods of days or weeks [1,2]. This slow, but precise regulation allows the body weight of an individual to fluctuate around a stable mean [3,4]. Various hypotheses have been put forward as to the feedback signal that would allow body weight to be controlled including mechanisms that regulate blood glucose [5], amino acids [6] or body temperature [7]. In 1953, Kennedy proposed the lipostatic theory [8] in which food intake is controlled by the hypothalamus to regulate body fat stores and over time it has become accepted that changes in the body weight of an adult are primarily determined by changes in body fat mass. This hypothesis requires that the hypothalamus detects the size of fat stores and parabiosis studies with hypothalamic obese rats [9] and genetically obese mice [10] demonstrated the presence of a humoral factor in the feedback regulation of body fat content. In 1994, Friedman's group [11] identified this circulating factor as ob protein which is now more commonly known as leptin.

1.1. Leptin production

The primary site of leptin production is white adipose tissue [11], although it is also expressed in several other tissues including the stomach [12], lungs [13], placenta [14] and possibly the brain [15]. In rodent adipose tissue leptin expression becomes apparent after differentiation of preadipocytes to adipocytes coinciding with early stages of lipid accumulation in the cells [16]. Expression is low during suckling, but increases rapidly after weaning [17]. The rate of increase in expression is proportional to white fat mass [18,19] and, although leptin expression varies between different fat depots [20,21], it shows a strong correlation with adipocyte size [22]. Leptin is continuously secreted, however, the rate of secretion may be increased or decreased independently of regulation of leptin mRNA expression [23] due to the presence of small vesicular stores of leptin in adipocytes [24,25]. Sustained stimulation of secretion requires a simultaneous increase in leptin mRNA expression to prevent rapid exhaustion of these leptin stores [23].

As noted above circulating concentrations of leptin increase in proportion to the size of white fat depots [18], but release is pulsatile [26] and there are diurnal oscillations in leptin release independent of weight related changes in circulating leptin. In humans leptin is higher at night than during the day [27] and may be entrained by meal consumption [28,29]. The response to a meal is greater at night than in the morning, and also correlates with the glycemic index of the meal [30]. By contrast, fasting [31] or cold exposure [32] inhibit leptin

☆ This article is part of a Special Issue entitled: Modulation of Adipose Tissue in Health and Disease.

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http://dx.doi.org/10.1016/j.bbadis.2013.05.009

production and release. Increases in leptin expression and secretion from adipocytes have been linked to insulin stimulation [23], cell glucose uptake [33] and the availability of energy substrates [34], all of which are indicative of an anabolic state. Activation of β-adrenergic receptors [35], or elevation of intracellular cAMP inhibit leptin expression [36] as does exposure to free fatty acids [37,38], each of which may be indicative of a state of energy mobilization. Detailed reviews of the regulation of leptin expression and secretion have been provided by Szkudelski [39] and by Lee and Fried [40].

1.2. Leptin receptors

There are multiple isoforms of the leptin receptor (ObRa-ObRe) [41] that have the structure of Class I cytokine receptors [42]. The different receptor subtypes have different length intracellular sequences and ObRb is the only receptor that includes binding domains necessary for JAK-STAT signaling. This long-form receptor (ObRb) has been shown to activate the transcription factors signal transducer and activator of transcription (STAT) 1, 3, 5 and 6 [43,44] in addition to phosphorylating phosphoinositide 3-kinase (PI3K) [45], mitogen activated protein kinases (MAPK) 1 and 2 [46] and increasing insulin receptor substrate-1 (IRS-1) and IRS-2-associated PI_3K [44]. Disruption of the STAT3 binding site on ObRb results in hyperphagia, a reduced energy expenditure and a degree of obesity that is equivalent to that in mice that are deficient in ObRb [47]. Therefore, activation of STAT3 is commonly used as a marker of leptin receptor activation. ObRa, ObRc, and ObRd have short intracellular domains and it is suggested that their primary functions are to transport leptin across the blood brain barrier [48] and to mediate lysosomal degradation of leptin [49]. ObRe is a circulating receptor that is produced by cleavage of the extracellular domain of both long and short-form leptin receptors [50,51]. ObRe sequesters leptin in the circulation [52] and can therefore regulate leptin bioactivity [53,54]. In lean subjects the amount of leptin that is bound to ObRe predominates over free leptin [55], but with the development of obesity the concentration of free leptin increases while bound leptin does not change. Brabant et al. [56] reported that free and bound leptin are released from adipose tissue in proportion to their concentrations in the circulation, and at least some of the leptin secreted from adipocytes is already bound to ObRe.

Leptin receptors are expressed on a majority of tissues and high concentrations have been identified in the arcuate nucleus of the hypothalamus [57], lung, liver, spleen, kidneys, adrenal [58] and reproductive tissues [59]. Lower concentrations have been identified in multiple peripheral tissues including adipocytes [60] where receptors have been detected both as mRNA and long- and short-form protein. These include hypothalamic nuclei, the raphe nucleus, the hippocampus, the amygdala, the ventral tegmental area, the area postrema and the nucleus of the solitary tract [57], and many areas of the brain that contribute to the control of food intake or energy expenditure. Although the level of leptin receptor expression is low in adipocytes, both mRNA [61–63] and protein [64–66] have been detected in various species, demonstrating the presence of long- and short-form receptors [65,66] which were reported to be located on the cell membrane and in small cytoplasmic vesicles in adipocytes [64]. Because adipocytes express leptin receptors [64] and receive sympathetic innervation [67] it is possible for leptin to have direct effects on adipocyte development and function, but also to indirectly modify adipocyte metabolism both through central mechanisms and via modification of release and function of metabolically active hormones, such as insulin.

The expression of ObR on T cells [68], B cells [69], monocytes and macrophages [70] indicates the potential for leptin to play an important role in both innate and acquired immune responses, as discussed in recent reviews [71,72]. Both in vivo [73] and in vitro [74] studies indicate that leptin has pro-inflammatory properties. Of relevance to this review is that obesity is recognized as a chronic low-grade inflammatory condition [75] and that pro-inflammatory cytokines contribute to the associated development of insulin resistance [76]. Experimental measures in humans [77] demonstrate a correlation between adipose tissue leptin expression and markers of inflammation, therefore the environment within obese adipose tissue appears to be one in which hyperleptinemia has the potential to promote inflammation and indirectly influence adipocyte metabolism.

1.3. Leptin resistance

Although the first animal experiments clearly demonstrated that leptin could inhibit food intake and weight gain and reduce body fat mass in both lean and obese, leptin deficient ob/ob mice [78–80], it soon became clear that leptin had no effect on food intake or body composition of animals that expressed leptin receptors, but were obese and had elevated circulating concentrations of endogenous leptin [81,82]. This condition is referred to as leptin resistance. More recently it has been shown that the failure to change food intake in response to leptin administration may reflect the development of leptin resistance in specific hypothalamic nuclei [83]. This suggests that only select actions of leptin are abolished by leptin resistance and in support of this Enriori et al. [84] reported that leptin continued to stimulate sympathetic outflow to brown fat in diet induced obese mice that were resistant to the effects of leptin on food intake. In parallel with the development of central leptin resistance Wang et al. [85] have proposed that white adipose tissue develops a local leptin resistance which may partially explain why high circulating concentrations of leptin in obese animals have little effect on white adipose tissue mass. They also [86] reported that activation of STAT3 was diminished in adipose tissue from leptin resistant diet induced obese rats in both basal and leptin stimulated conditions. The resistance was associated with an early elevation of suppressor of cytokine signaling (SOCS) 1 and 3 expression, which inhibits activation of JAK/STAT3 [87], followed by suppression of ObRb expression [86]. Similarly it has been reported that leptin receptor expression is greatly reduced in adipose tissue from morbidly obese women [88], but SOCS3 is also suppressed, possibly because of a reduced need to inhibit cytokine signaling. As discussed below, although leptin has little direct effect on adipocyte glucose metabolism, there is evidence for leptin modifying adipocyte insulin responsiveness [89] and for maintaining basal rates of liplysis [90], therefore, leptin resistance at the level of the adipocyte may contribute to changes in the ability of fat cells to regulate triglyceride turnover. Thus, the development of leptin resistance is more complicated than just modification of leptin transport into the brain [91] or a change in responsiveness of receptors in specific brain sites [83,84]. Identifying factors associated with the development and consequences of leptin resistance may lead to a better understanding of how leptin influences the metabolic and physiologic state of an animal in conditions of obesity.

2. Evidence for a direct effect of leptin on adipose tissue metabolism

The focus of this review is the effect of leptin on adipocyte metabolism. Relatively little has been published related to an investigation of the effects of leptin on adipocyte metabolism compared with the large number of studies that have examined the effects of central or peripheral leptin administration on whole animal energy balance. Adipose tissue expresses both long- and short-form receptors [60] providing the potential for self-regulation of leptin expression [92,93] in addition to direct metabolic effects of leptin on adipocytes. As discussed below, the change in metabolism may also be achieved indirectly through modification of release of metabolically active hormones, changes in response to these hormones or by increasing the activity of sympathetic afferents to the fat cell. Administration of leptin to leptin-responsive animals reduces body fat mass [94], therefore there must be a shift in the balance between lipolysis and lipogenesis to favor lipid mobilization.

Please cite this article as: R.B.S. Harris, Direct and indirect effects of leptin on adipocyte metabolism, Biochim. Biophys. Acta (2013), http://dx.doi.org/10.1016/j.bbadis.2013.05.009