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The neuroanatomical function of leptin in the hypothalamus

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ABSTRACT

The anorexigenic hormone leptin plays an important role in the control of food intake and feeding-related behavior, for an important part through its action in the hypothalamus. The adipose-derived hormone modulates a complex network of several intercommunicating orexigenic and anorexigenic neuropeptides in the hypothalamus to reduce food intake and increase energy expenditure. In this review we present an updated overview of the functional role of leptin in respect to feeding and feeding-related behavior per distinct hypothalamic nuclei. In addition to the arcuate nucleus, which is a major leptin sensitive hub, leptin-responsive neurons in other hypothalamic nuclei, including the, dorsomedial-, ventromedial- and paraventricular nucleus and the lateral hypothalamic area, are direct targets of leptin. However, leptin also modulates hypothalamic neurons in an indirect manner, such as via the melanocortin system. The dissection of the complexity of leptin's action on the networks involved in energy balance is subject of recent and future studies. A full understanding of the role of hypothalamic leptin in the regulation of energy balance requires cell-specific manipulation using of conditional deletion and expression of leptin receptors. In addition, optogenetic and pharmacogenetic tools in combination with other pharmacological (such as the recent discovery of a leptin receptor antagonist) and neuronal tracing techniques to map the circuit, will be helpful to understand the role of leptin receptor expressing neurons. Better understanding of these circuits and the involvement of leptin could provide potential sites for therapeutic interventions in obesity and metabolic diseases characterized by dysregulation of energy balance.

1. Introduction

1.1. Leptin

The anorexic hormone leptin is the product of the ob gene which is localized on the mouse and human chromosomes 6 and 7q31.3, respectively (Friedman et al., 1991; Green et al., 1995). Leptin is primarily expressed in white adipose tissue (Zhang et al., 1994) and functions as an afferent signal in the regulation of body weight, food intake and energy expenditure (Halaas et al., 1995; Pelleymounter et al., 1995). Circulating leptin concentrations are broadly proportional to the total amount of body fat and BMI (body mass index) in both rodents and humans (Considine et al., 1996; Maffei et al., 1995). As such, circulating leptin and leptin mRNA levels are highly correlated to energy stores in adipose tissue (Considine et al., 1996; Frederich et al., 1995; Maffei et al., 1995). In addition, overfeeding leads to elevated leptin levels whereas fasting reduces leptin availability (Kolaczynski et al., 1996; Saladin et al., 1995). Another factor that determines the level of circulating leptin is the size of the adipocytes. Larger adipocytes contain more

Abbreviations: AgRP, agouti related protein; Alpha-MSH, α-melanocyte-stimulating hormone; Arc, arcuate nucleus; AVP, arginine-vasopressin; BAT, brown adipose tissue; BBB, blood–brain-barrier; BDNF, brain derived neurotrophic factor; BNST, bed nucleus of the stria terminalis; CART, cocaine and amphetamine regulated transcript; CRH, corticotropin releasing hormone; DMH, dorsomedial hypothalamus; Dyn, dynorphin; GABA, γ-aminobutyric acid; Gal, galanin; GALP, galanin-like peptide; GFP, green fluorescent protein; HPA, hypothalamic–pituitary–adrenal; HPT, hypothalamic–pituitary–thyroid; iBAT, interscapalur brown adipose tissue; icv, intracerebroventricular; IML, intermediolateral; LH, lateral hypothalamus; LS, lateral septum; MCH, melanin-concentrating hormone; ME, median eminence; NAc, nucleus accumbens; NPY, neuropeptide Y; NTs, neurotensin; NTS, nucleus of the solitary tract; OR, orexin; OXT, oxytocin; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; rRPa, raphe pallidus; SF-1, steroidogenic factor 1; SNA, sympathetic nervous activity; SNS, sympathetic nervous system; SON, supraoptic nucleus; TRH, thyroid releasing hormone; TrkB, tyrosine receptor B; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

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leptin in comparison with smaller adipocytes in the same individual (Considine et al., 1996; Madej et al., 1995).

An important factor in leptin-mediated signaling is the passage of leptin across the blood–brain barrier. This is through active transport as leptin is too large to cross the blood–brain-barrier (BBB) by simple diffusion. The relatively permeable BBB of the arcuate nucleus (Arc) and median eminence (ME) enables leptin to enter the mediobasal hypothalamus (Banks et al., 1996) where it acts on the leptin receptor. It has been suggested that leptin is transported across the BBB in a dose-dependent manner by a unidirectional saturable system (Banks et al., 1996; Burguera and Couce, 2001; Maness et al., 1998). The short form of the leptin receptor, which is abundantly found at the BBB, has been indicated to be involved in the transport of leptin across the BBB (Bjørbæk et al., 1998; Boado et al., 1998; Kastin et al., 1999). Interestingly, Prevot and colleagues recently established a new physiological concept in the regulation of energy homeostasis. These authors showed that the nutritional status of an individual modulates the permeability of the blood–hypothalamus barrier allowing metabolic hormones to directly access a subset of Arc neurons. The Arc lies adjacent to the ME, which contains a blood–cerebrospinal fluid barrier composed of tanycytes, specialized ependymal cells located in the floor of the third ventricle, which allows for passive and rapid transport of circulating leptin into the medial basal hypothalamus (Prevot et al., 2013). The close proximity of the arcuate to the BBB, makes the arcuate nucleus a specially sensitive site for leptin. An unresolved question is how far leptin penetrates to other hypothalamic nuclei that express leptin receptors and whether the leptin predominantly enters the brain at sites where the BBB is thin, like near the arcuate nucleus.

1.2. Leptin receptor binding

The *db* gene encodes the leptin receptor (Ob-R), which belongs to the class I cytokine receptor family (Tartaglia et al., 1995). Several isoforms of the Ob-R are produced by alternative splicing and at least six isoforms designated Ob-Ra-f, have been identified so far. The short form receptors, i.e. Ob-Ra, Ob-Rc, Ob-Rd and Ob-Rf, have been implicated in the transport of leptin across the BBB, as they are mainly expressed in the choroid plexus, vascular endothelium and peripheral tissues (Bjørbæk et al., 1998; Elmquist et al., 1998b; Kastin et al., 1999). The Ob-Re is a soluble receptor that enhances leptin's half-life (Abbott et al., 2000; Bittencourt and Elias, 1998; Huang et al., 2001; Lammert et al., 2001; Yang et al., 2004) and serves as an antagonist of the transport of leptin (Tu et al., 2007). The long isoform Ob-Rb contains intracellular motifs necessary for activating the JAK/STAT signal transduction pathway (Bjørbæk et al., 1997) and is therefore essential for the physiological action of leptin in the hypothalamus, where it is expressed at high levels (Elmquist et al., 1998b). As the long isoform is the only functional leptin receptor in the brain this review will focus on its distribution and function.

Unliganded Ob-Rb exists as a pre-formed homodimer. Each receptor can bind one leptin molecule with high affinity (Fong et al., 1998; Tartaglia et al., 1995). Upon leptin binding, the conformation of the Ob-Rb dimer changes, enabling transphosphorylation and activation of intracellular Ob-Rb-associated JAK2 molecules (Couturier and Jockers, 2003; Devos, 1997; Tartaglia, 1997). Furthermore, the intracellular domain of the Ob-Rb contains a binding site for the transcription factor signal transducer activator of transcription (STAT) proteins, including STAT3 (Bates and Myers, 2003), and mediates the translocation of STAT3 into the nucleus where it promotes the transcription of several genes, including suppressor of cytokine signaling 3 (SOCS3) (Bjorbak et al., 2000; Dunn et al., 2005). Leptin receptor activity is negatively regulated by its own activity (Dunn et al., 2005) as SOCS3 suppresses the activity at the level of Tyr 985 and Box1 motif (Endo et al., 1997; Münzberg and Myers, 2005; Shimizu et al., 2007; Starr et al., 1997). In addition, the non-transmembrane enzyme phosphatase protein 1B (PTP1B) inhibits the activity of Ob-Rbs at the level of the Box1 motif (Zabolotny et al., 2002). Direct and indirect activation of the JAK/STAT pathway activates multiple signaling pathways involving the activation of kinase-induced phosphorylation of proteins, including JAK2/STAT3, phosphoinositide 3-kinase (PI3K), extracellular signal-regulated kinase (ERK) and insulin receptor substrate 1 (IRS1). Interestingly, leptin directly activates PI3K in POMC neurons while inducing an opposite effect in AgRP neurons (Xu et al., 2005). For a more detailed overview of the intracellular signaling pathways activated by leptin (see Frühbeck, 2006; Myers, 2004).

1.3. Leptin receptor distribution

The functional importance of the hypothalamus for leptin's role in energy homeostasis stems from its high leptin-receptor density in both rodents and humans (Elmquist et al., 1998b; Hâkansson et al., 1998; Schwartz et al., 1996), enabling leptin to modulate a neuronal activity across multiple brain areas and cell types. In particular, leptin receptors are abundantly expressed in hypothalamic nuclei involved in the regulation of energy homeostasis including the Arc, ventromedial nucleus, dorsomedial hypothalamus and the lateral hypothalamic area (Elmquist et al., 1998b; Hâkansson et al., 1998; Håkansson and Meister, 1998; Mercer et al., 1996; Schwartz et al., 1996). In addition, Ob-R mRNA is also expressed in various degrees in extra-hypothalamic regions, including the cerebellum, hippocampus, amygdala, brains stem and substantia nigra (Elmquist et al., 1998b; Figlewicz et al., 2003; Grill and Kaplan, 2002; Hâkansson et al., 1998; Mercer et al., 1996).

1.4. Hypothalamus

The hypothalamus serves as the primary site for the integration and regulation of a multitude of physiological processes, including thermoregulation, metabolism, and body weight, aspects of cardiovascular function, physiologic adaptation to stress, regulation of growth and reproduction (including sexual behavior). Hypothalamic nuclei receive information from peripheral tissue through nervous connections, the bloodstream and the cerebrospinal fluid and respond to inputs via the same routes. The role of the hypothalamus in the regulation of body weight and food intake was established by lesion studies, highlighting the involvement of the Arc, the ventromedial- (VMH), and dorsomedial hypothalamus (DMH), the paraventricular nucleus (PVN) and the lateral hypothalamus (LH). All of which are areas that express the leptin receptor (Elias et al., 2000; Hâkansson et al., 1998). In the following sections we will describe several of the key hypothalamic nuclei and outline the role of leptin signaling in their function. Although it is clear that leptin serves a multitude of functions, we will focus in this review on its role in feeding behavior and energy homeostasis. For more elaborate overview of the neural circuits involved in regulating feeding behavior see (Schwartz and Zeltser, 2013). Although various leptin-receptor expressing cell-types are found across multiple brain areas, in this review we will describe known cell-type specific modulation by leptin per hypothalamic area. Where possible we will elaborate on the functional consequences of leptin signaling. A detailed neuroanatomical map of leptin-receptor distribution is presented in Fig. 1. Table 1 presents an overview of the neuropeptides involved in energy balance with respective receptor expression and projections.