Journal of Chemical Neuroanatomy 61-62 (2014) 256–265

Contents lists available at ScienceDirect

Journal of Chemical Neuroanatomy

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

Leptin action in the midbrain: From reward to stress

Lu Xu *

Department of Anatomy, Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

ARTICLE INFO

Article history:
Received 9 April 2014
Received in revised form 13 June 2014
Accepted 25 June 2014
Available online 5 July 2014

Keywords:
Nutrition status
Midbrain
Dopamine neurons
Addiction

ABSTRACT

The midbrain is a heterogenous brain structure that serves important roles in feeding regulation, motivation and reward, movement and stress adaptation. One common feature of different midbrain regions is that they all express the long form of leptin receptor (LepRb). Leptin is mainly produced and secreted by white adipose tissue, informing the brain centers *via* LepRb about the amount of fat storage in the body. In this way, leptin exerts its action in the midbrain to regulate different functions. First, this review deals with the basic information of leptin and its signaling. Then, attention is given to various interactions of leptin with the midbrain regions, including ventral tegmental area (VTA), substantia nigra pars compacta (SNc), rostral linear raphe (RLi) and centrally-projecting Edinger–Westphal nucleus (EWcp). Also, the projection areas of these midbrain regions are discussed. Finally, the possible function of leptin in the midbrain is suggested.

Introduction

The worldwide incidence of overweight and obesity is rapidly increasing. Obesity predisposes individuals to cardiovascular disease and type-2 diabetes, reduces life expectancy and incurs high costs for society. Unfortunately, overweight is very difficult to treat. In most cases, calorie-restricting diets, even in combination with behavioral techniques and exercise, do not result in lasting weight loss (Mann et al., 2007), which is most likely due to the dysregulation of homeostatic mechanisms (Bose et al., 2009; Cornier, 2011). In recent years there has been tremendous progress in deciphering how the homeostatic system in the hypothalamus modulates appetite and metabolism and thereby regulates body weight (Abizaid et al., 2006; Morton et al., 2006; Karatsoreos et al., 2013). However, understanding this system is not enough to solve the problem of obesity because neural circuits that are superimposed on this system can override the homeostatic signals, resulting in changed patterns of weight regulation (Schank et al., 2012). The motivation to eat or to stop eating and the bidirectional feeding responses (stimulating or inhibiting) to various (psychological) stressors all underline the complexity of the neural and neuroendocrine mechanisms that together regulate body weight. To obtain a better insight into this complexity, research on feeding control has recently extended its focus from the hypothalamus to additional important brain circuits controlling emotion, cognition and motivated behavior, and to the central and peripheral signals that modulate the activity of these circuits. As a result, novel data have accumulated that 'feeding peptides' such as leptin, insulin, peptide YY, cholecystokinin and ghrelin, not only influence feeding circuits but also interact with circuits involved in reward, cognitive or stress response. In the current review, we focus on the one of these peptides, the peripheral peptide leptin.

The leptin/LepRb system

Leptin is a 16 kDa adipose-derived adipokine that modulates a variety of behaviors and physiological functions, such as reducing food intake, increasing energy expenditure, regulating body weight and stimulating reproduction (Campfield et al., 1995; Halaas et al., 1995; Pelleymounter et al., 1995; Levin et al., 1996; Ahima and Osei, 2004; Bouret and Simerly, 2007; Myers et al., 2009; Zuure et al., 2013; Elias, 2014). The peptide from adipose tissues circulates *via* the blood to enter the brain, where it conveys information about the amount of peripherally stored fat (Zhang et al., 1994). In this way the leptin concentration informs brain centers about how much energy the body has as a reserve (Maffei et al., 1995). The crucial role of leptin in energy homeostasis is revealed by the fact that mice deficient for leptin (*ob*/*ob*) exhibit severe hyperphagia and profound obesity (Chua et al., 1996; Elmquist et al., 1999). Exogenous leptin reverses these effects and restores energy balance in such mutants (Ahima et al., 1996).

* Tel: +31 243614271; fax: +31 243613789.
E-mail addresses: lu.xu@radboudumc.nl, xulu6769@gmail.com

http://dx.doi.org/10.1016/j.jchemneu.2014.06.007
0891-0618/

The effects of leptin are mediated by the leptin receptor (LepR). Deficiency of this receptor in the central nervous system (CNS) promotes hyperphagia and decreases energy expenditure (Cohen et al., 2001; Bates et al., 2004; Dhillon et al., 2006). Although alternative splicing of the LepR (*db*) gene generates six isoforms (Chen et al., 1996; Ahima and Osei, 2004), the receptor long form, LepRb, is thought to be crucial for the peptide's action because LepRb contains a fully signaling-competent intracellular domain. Leptin binding to LepRb activates typically the Janus kinase 2 (JAK2)-signal transducer and activator of transcription 3 (STAT3) pathway (Ghilardi et al., 1996; Villanueva and Myers, 2008). Mice deficient specifically for LepRb display similar phenotype as the *ob*/*ob* mice (Robertson et al., 2008), and transgenic expression of LepRb in the brain of mice deficient for all LepR isoforms almost fully restores leptin's actions (Chua et al., 2004). Thus, LepRb-expressing neurons in the brain represent the major cellular mediators of leptin action.

The distribution of LepRb in the brain has been well studied using a variety of methods, such as genetic analysis and *in situ* hybridization, and these studies have revealed large numbers of LepRb neurons in discrete hypothalamic nuclei as well as in midbrain regions, brainstem and a few other brain regions (Elmquist et al., 1998; Leshan et al., 2006; Scott et al., 2009). The identification of LepRb neurons reveals the direct targets of leptin action in the brain, and suggests that discrete populations of LepRb neurons may contribute to distinct aspects of central leptin action. Furthermore, by the functional analysis of some populations of LepRb neurons, leptin function is found to be dependent also on the subtype of LepRb-expressing neurons and their projection areas. This notion is supported by the fact that local populations of LepRb neurons that differ in their neurochemical make-up, do exert different functions. For example, LepRb-containing neurons of the ventral medial hypothalamus (VMH) that produce steroidogenic factor-1 contribute to leptin control of energy homeostasis by modifying energy expenditure (Dhillon et al., 2006), whereas LepRb/pro-opiomelanocortin (POMC)-expressing neurons in the arcuate (ARC) are important for regulating glucose homeostasis (Balthasar et al., 2004; Elmquist et al., 2005; Gao and Horvath, 2007), and furthermore, LepRb/agouti-related protein/neuropeptide Y (AgRP/NPY)-expressing neurons strongly induce feeding suggesting that they have a rather prominent role in satiety (Aponte et al., 2011; Wu and Palmiter, 2011). Therefore, it seems important to characterize each population of LepRb-expressing neurons to determine their specific contribution to leptin action.

This does not only hold for the 'traditional' hypothalamic nuclei involved in feeding and energy expenditure, but also for a number of extrahypothalamic areas. In addition to regulating satiety, leptin controls the incentive value of food and other rewards and suppresses depression and anxiety-like behavior (Fulton et al., 2000; DiLeone et al., 2003; Figlewicz et al., 2006; Lu et al., 2006; Liu et al., 2010). For instance, the mesolimbic dopamine (DA) system that arises from dopaminergic neurons in the ventral tegmental area (VTA), mediates important aspects of incentive salience for food but also contributes to aspects of emotion and behavior (DiLeone et al., 2003; Kelley et al., 2005; Nestler, 2005). Furthermore, the centrally-projecting Edinger–Westphal nucleus (EWcp) urocortin 1 (Ucn1) system is involved in the stress response and anxiety- and depression-like behavior. These midbrain regions, VTA, EWcp, together with the rostral linear raphe (RLi) and the substantia nigra pars compacta (SNc), all originate from the midbrain floor plate (Joksimovic et al., 2009) and all express LepRb (Scott et al., 2009). The shared phenotype and common origin of these midbrain nuclei suggest an important coordinating role for leptin in the midbrain. In this review, we will describe the characterization of midbrain LepRb neurons, as well as how leptin regulates these neuron populations to contribute to total leptin action.

The VTA

The dopaminergic neurons in the VTA and their targets in the nucleus accumbens (NAc) and in the medial prefrontal cortex (mPFC), form together with the hippocampus and the amygdala what is often considered as the brain's mesocorticolimbic "reward circuit" (Robinson and Berridge, 2003; Vezina, 2004; Hyman et al., 2006). For long, this system has been investigated primarily for its role in motivated behaviors and reinforcement learning and its dysfunction has been related to disorders like addiction, schizophrenia and depression. On the basis of recently developed new anatomical, physiological and behavioral approaches, new data indicate that the DA-system in the VTA is more heterogenous than previously assumed and that the function of this system strongly depends on its axonal projection patterns and the connectivity and functional properties of its synaptic contacts (Carr and Sesack, 2000; Margolis et al., 2006, 2012; Fields et al., 2007; Yamaguchi et al., 2007; Luo et al., 2008; Lammel et al., 2012; Roeper, 2013). An account of the detailed investigations of the specificity and plasticity of the mesolimbic system is beyond the scope of this review (for reviews, see *e.g.* Opland et al., 2010; Volman et al., 2013), but as the main function ascribed to the VTA system is in reward control, we will focus on the nature and possible underlying mechanisms of leptin's action on this process.

Leptin and food reward

Evidence is accumulating that leptin affects feeding behavior independently of its actions on the hypothalamus. Infusion of leptin directly into the VTA results in an increase in JAK2-STAT3 signaling, an event critical for leptin's action in the VTA to decrease chow feeding (Morton et al., 2009). Also, injection into the VTA of a virus that expresses an RNA designed to inactivate leptin receptor expression leads to increased food intake (Hommel et al., 2006). Although these rats ate more, they did not gain weight, perhaps because they also increased their energy-consuming, night-time locomotor activity. In any case, these experiments are consistent with the idea that leptin signaling in the VTA normally suppresses food intake and locomotor activity.

Given the key role of VTA in reward behavior, the demonstration of leptin's anorexigenic effects led to a number of studies on the peptide's role in food reward. Conditioned place preference (CPP) is a classical test in addiction research to show rewarding properties of a substance (*e.g.* cocaine, amphetamine, alcohol; Carr et al., 1988; Hemby et al., 1992; Ciccocioppo et al., 1999), and has also been used to assess the rewarding properties of food (Guyon et al., 1993; Lepore et al., 1995; Perks and Clifton, 1997). Leptin appears to block the CPP response to a high-fat diet, by shortening the time animals spend in an environment previously paired with high-fat diet (Figlewicz et al., 2004). Moreover, leptin reverses the food-deprivation-induced CPP response by sucrose pellets (Figlewicz et al., 2001). Importantly, viral knock down of LepR in the VTA increases preference for sucrose and for high-fat diets (Hommel et al., 2006). The progressive ratio (PR) operant conditioning procedure is another test that assesses a substance's motivational properties, letting an animal work progressively harder to obtain a primary reinforcer (*e.g.* cocaine or sugar). Ventricular leptin injections decrease performance on a PR task to obtain sugar, indicating that leptin decreases food-motivated behavior (Figlewicz et al., 2006). These data together suggest an involvement of VTA in leptin's effect on reduced food reward.