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Lateral thinking about leptin: A review of leptin action via the lateral hypothalamus ☆

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ABSTRACT

The lateral hypothalamic area (LHA) was initially described as a "feeding center" but we are now beginning to understand that the LHA contributes to other aspects of physiology as well. Indeed, the best-characterized neuronal populations of the LHA (which contain melanin-concentrating hormone (MCH) or the hypocretins/orexins (OX)) are not strictly orexigenic, but also have roles in regulation of the autonomic and sympathetic nervous systems as well as in modulating motivated behavior. Leptin is an anorectic hormone that regulates energy homeostasis and the mesolimbic DA system (which transduces the wanting of food, drugs of abuse, and sex) in part, via actions at the LHA. At least three populations of LHA neurons are regulated by leptin: those containing MCH, OX or the long form of the leptin receptor, LepRb. The emerging picture of leptin interaction with these LHA populations suggests that the LHA is not merely regulating feeding, but is a crucial integrator of energy balance and motivated behavior.

1. Why do we need to think about feeding and energy balance?

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 $117 billion in annual health care costs in the U.S. alone [1,2]. The only proven disease-modifying treatments for obesity are dietary regulation and weight loss. Bariatric surgery has been used with some success to potentiate weight loss, but this method is invasive, requires permanent lifestyle modifications and sustained weight loss is not guaranteed — some subjects regain weight in the years after surgery [3,4]. The more conventional methods for weight loss are diet and exercise, supported by a multi-billion dollar industry and a staggering number of new supplements, diet plans and exercise regimes each year [5]. In spite of this, most dieters ultimately regain weight and these methods have poor long-term success rates. Indeed, this demonstrates that the body staunchly defends against negative changes in homeostatic set point, but is unable to defend against positive changes, resulting in progressive weight gain. Pharmacologic therapies to reduce appetite and increase energy expenditure would be useful treatments, but limited understanding of the physiologic systems regulating these processes has hindered development of truly effective therapies to treat or prevent obesity. As a result, there has been a surge of research focused on systems that impact energy homeostasis and how these might be tenable targets for therapeutic intervention.

2. The leptin/LepRb system is a crucial regulator of energy homeostasis

2.1. Leptin

In 1950 the Jackson Laboratory identified a mouse line displaying profound hyperphagia, obesity, infertility and severe hyperglycemia resulting in diabetes. Nearly five decades later the genetic deficit underlying this phenotype was found to be a mutation on chromosome 6 in the obese (*ob*) gene and its gene product, leptin [6]. Leptin is a hormone produced by adipocytes and secreted into the circulation. Importantly, leptin is produced in proportion to peripheral energy reserves (i.e. fat), so leptin concentration indicates how much energy the body has on board [7]. The crucial role of leptin in energy homeostasis is revealed by the hyperphagic and obese phenotypes of leptin-deficient rodents and humans, which are normalized with leptin treatment [8,9]. Leptin also has an important role in the regulation of glucose homeostasis, reproduction, growth, the immune response and motivated behaviors, such as intake of food and drugs of abuse and locomotor activity [10–12].

2.2. LepRb

Another obese mouse was discovered in 1965, with a genetic mutation that mapped to chromosome 4: this became known as the *db*/*db* mouse [13–15]. Coleman and colleagues characterized the differences between the obese *ob*/*ob* and *db*/*db* lines by joining the circulatory systems of these mice with normal mice or each other and

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observing the resulting phenotype, a technique called parabiosis (reviewed in [14]). Parabiosis of an *ob*/*ob* mouse with a normal lean mouse caused the *ob*/*ob* to lose weight, due to restoration of a missing circulatory factor provided by the lean mouse — this turned out to be leptin. By contrast, parabiosis of a *db*/*db* and normal lean mouse did not cause weight loss in the *db*/*db*, suggesting that this obese phenotype was not due to lack of circulating leptin but perhaps something necessary to transduce the leptin signal. Indeed, later experiments verified that the *db* gene encodes the long form of the leptin receptor (LepRb) [13,16]. Leptin acts by binding to cells expressing LepRb, the only leptin receptor isoform containing the intracellular motifs required to convey leptin signals [15,17–19]. Rodents lacking LepRb (i.e. *db*/*db* mice and *fa*/*fa* rats) recapitulate the phenotype of leptin-deficient models (obese, hyperphagic, infertile, diabetic), demonstrating the necessity of leptin signaling via LepRb [13,16,20].

The central action of leptin is crucial for energy balance and mediated via distributed populations of LepRb-expressing neurons throughout the brain [21–24]. There are several LepRb neuronal populations within the midbrain, including the dorsal raphe (DR) and periaqueductal gray (PAG), linear raphe, Edinger–Westphal nucleus and LepRb neurons in the ventral tegmental area (VTA). [24,25]. There are also populations of LepRb neurons ranging from rostral brain areas such as the medial preoptic area (mPOA) to the caudal extent of the brain, in the hindbrain nucleus of the solitary tract (NTS). The hypothalamus, however, contains the largest density of LepRb neurons, distributed among mediobasal areas (e.g. arcuate (ARC) and ventromedial (VMH) nuclei), the ventral premammillary nucleus (PMv), the dorsomedial hypothalamus (DMH) as well as the lateral hypothalamic area (LHA).

2.3. The "distributed function hypothesis" and leptin action

Brain function is often defined by region; for example, sensation is processed in somatosensory cortex, while motor control is regulated via separate motor cortex. The observation that LepRb-expressing neurons are broadly distributed throughout many different brain areas suggested that discrete populations of LepRb neurons may contribute to distinct aspects of central leptin action [10,11]. This concept has been termed the "Distributed Function Hypothesis" of leptin action, and is supported by the fact that regional populations of LepRb neurons differ in their molecular and/or neurochemical expression. For example, LepRb/SF1-containing neurons of the VMH contribute to leptin control of energy homeostasis by modifying energy expenditure. Adjacent LepRb/pro-opiomelanocortin (POMC)-expressing neurons in the ARC are crucial for regulating glucose homeostasis [26–32]. By contrast, the opposing LepRb/agouti-related protein/neuropeptide Y (AgRP/NPY)-expressing neurons strongly induce feeding, suggesting that they have a more prominent role in satiety [33–35]. The role of other LepRb neuronal populations has not been studied as extensively, but has unique molecular profiles that suggest additional specificity. For example, tyrosine hydroxylase (TH), the rate-limiting enzyme in dopamine (DA) synthesis, is expressed in LepRb neurons of the VTA that project to the central amygdala [25,36,37]. Additionally, a population of mediobasal LepRb neurons contain neuronal nitric oxide (nNOS) and LepRb neurons in the Edinger Westphal nucleus contain urocortin-1 [38,39]. Molecular characterization of LepRb-expressing populations has enabled site-specific examination of the role of leptin, and so we are beginning to identify the populations of LepRb neurons that contribute to various aspects of leptin action. LepRb neurons of the ARC and NTS are important for leptin-mediated satiety [26,39–41]. Leptin contributes to glucose homeostasis via LepRb-POMC neurons of the ARC [29,32,42,43], while leptin action via the PMv regulates puberty and fertility [28,38,40–47]. In support of the "distributed function hypothesis," disruption of leptin signaling via a single population of LepRb neurons does not nullify total leptin action, but rather disrupts particular facets of leptin-control [26,28,32,37,47,48]. Thus, it will be important to characterize each population of LepRb-expressing neurons to illuminate their specified contribution to leptin action and energy homeostasis.

2.4. A role for leptin in the lateral hypothalamic area (LHA)

Upon the identification of LepRb much attention was devoted to understanding leptin action via the dense populations of LepRb-expressing neurons in mediobasal hypothalamic nuclei, such as the ARC and VMH. By comparison, much less was known about the nearby population of LepRb-expressing neurons in the LHA. In 1998 Elmquist et al. first reported a substantial number of LepRb neurons lying within the LHA, an area historically described as a "feeding center" [22]. Over the subsequent decade, many reports described leptin effects upon various LHA neuronal populations that altered energy homeostasis, but the role of leptin action via LepRb neurons in the LHA remained unclear. We have begun to characterize LHA LepRb neurons, as well as how leptin regulates these and other LHA neuronal populations to contribute to total leptin action. The remainder of this review will examine the neuronal populations and connectivity of the LHA and how leptin acts via the LHA to contribute to energy homeostasis and behavior.

3. The lateral hypothalamic area (LHA), then and now

3.1. Historical perspective: The LHA is a feeding center

Unlike the small, circumscribed mediobasal hypothalamic nuclei (e.g. ARC, VMH, and PMv), the LHA covers a broad lateral region throughout the extent of the hypothalamus. In the caudal and medial hypothalamus of rodents the LHA lies mainly above and lateral to the fornix. While not ostensibly different in cytoarchitecture, this portion of the LHA is often subdivided into the area just above and around the fornix (the perifornical area) or ventral to the fornix (the subfornical region), and these regions differ in their connectivity [49–51]. At the rostral extreme of the hypothalamus the LHA is predominantly lateral to the fornix and eventually merges into the lateral preoptic areas [52,53]. The medial forebrain bundle (mfb) extends through the LHA to the ventral striatum, directly linking the LHA with the DA signaling system. The LHA was originally described as a "feeding center" based on findings that LHA lesions produced extreme hypophagia (to the point of starvation) while electrical stimulation of the LHA promoted food intake even in sated animals [54–59]. At the same time, the LHA was characterized as a structure important in mediating reward, largely based on studies showing that animals with electrodes placed in the LHA will self-administer electrical current [60,61]. This paradigm of intracranial self-stimulation (ICSS) via the LHA is still used to determine how drugs of abuse and other stimuli affect DA signaling and brain reward systems [62]. While stimulation and action via the mfb (which runs through the LHA and contains mesolimbic DA fibers) might explain some of the initially observed behavior/reward effects, these reports yielded a flurry of exploration of the LHA and its role in intake and hoarding of food, salt appetite and drinking behaviors [63–65].

3.2. The connectivity of the LHA suggests its function

The initial characterization of the LHA as a center for food intake behaviors suggested that it must interact with brain regions that ultimately coordinate these behaviors (i.e. to couple LHA signals with learning/memory as well as systems required to execute feeding behavior). This line of thinking sparked an intense interest in mapping the neuronal connectivity of the LHA to better understand its functional role in neurophysiology and behavior. Interestingly, the

field has since determined that neurons in the LHA project widely throughout the brain and, via polysynaptic connections, also regulate targets outside of the brain. The LHA therefore modulates the autonomic and somatomotor systems, regulating targets including (but not limited to) skeletal and cardiovascular muscle, the adrenal gland and brown adipose tissue [66–69]. This regulation likely coordinates motivation with appropriate output at the periphery (i.e. muscle movements required to seek food, altered heart rate and blood pressure needed to support motor systems, and energy expenditure via brown adipose tissue).

LHA neurons also directly project to diverse regions within the brain. Mapping the projections from small mediobasal hypothalamic nuclei is challenging but this task is incredibly daunting for the large LHA, which spans nearly the entire hypothalamus. LHA afferents have been described throughout the rostral–caudal axis of the brain. Prominent innervation sites in the midbrain include the dorsal raphe (DR), periaqueductal gray (PAG) parabrachial nucleus, and VTA [70–72]. The LHA also projects to, and receives dense innervation from, the amygdala [73,74]. Rostral projection targets of the LHA include septal nuclei (such as the bed nucleus of the stria terminalis (BNST) and lateral preoptic area), the striatum (including the NAc) and pallidal regions [72]. Recent work from the laboratory of Larry Swanson has provided more detailed understanding of LHA connections by mapping the projections from sub-regions of the LHA, defined mainly by their proximity to the fornix [50,51]. Based on their findings, Table 1 summarizes some of the major LHA afferents based on their sub-region of origin. These elegant studies suggest that certain LHA sub-regions predominantly target, and presumably regulate, a limited number of specified brain regions. Additionally, some of these sub-regions appear to preferentially target aspects of the mesolimbic, corticolimbic or pallidal systems that have been implicated in motivated behaviors, such as intake of food and drugs as well as locomotor activity. For example, the caudal and medial region of the LHA (bordering the PVH) projects more densely to the striatum than the substantia innominata (pallidum). By contrast, the portion of the LHA just above the fornix sends dense projections to the substantia innominata and the VTA but fewer projections to the dorsal and ventral striatum. Further, most projections from the LHA area below the fornix do not target the VTA but send dense projections to the basomedial amygdala. These studies, along with identification of the types of neurons within each of these sub-regions, will provide crucial understanding of how the LHA regulates physiological and neural systems.

3.3. Current perspectives: The LHA regulates motivated behavior

The LHA is densely connected with many limbic structures (e.g. the VTA, striatum, and pallidum), which are important in the regulation and execution of motivated behaviors. Motivated behavior describes the locomotor activity or work that a subject exhibits and reflects the relative value of a stimulus (i.e. drugs of abuse, alcohol, food, and sex). For example, amphetamine treatment increases the locomotor activity of rodents, and quantitation of that activity is used as “read-out” of the motivational effect of the drug (as reviewed in [75]). Additionally, animals will learn to press levers or nose-poke to obtain palatable food, drugs or other wanted stimuli [76–79]. Motivated behaviors are regulated via dopamine (DA) neurons of the ventral tegmental area (VTA) that project to the nucleus

Table 1
Summary of major brain area projection targets of LHA by sub-region, adapted from [50,51]. Medial: refers to rostral LHA area that is adjacent to the PVH and medial to the fornix. Above F: area of the LHA that is lateral to the DMH and above the fornix. Below F, Rostral: anterior area of the LHA that is below the F. Below F, Caudal: posterior area of the LHA that is below the F. ND = projections not defined in this area, F = fornix.

	Medial	Above F	Below F, rostral	Below F, caudal
Motivated behavior				
Basomedial amygdala	ND	ND	++/+++	−
Dorsal striatum	+++	+	ND	ND
Ventral striatum (NAc)	+++	+	−	++
Substantia innominata (SI)	−	++++	+/++	++
Septal nuclei	+++/+	+++	ND	ND
BNST	+/++	++/+++	−	++/+++
VTA	−	+++	−	−
Lateral habenula (LH)	+++++	++	+/++	−
Thalamus				
Paraventricular nucleus (PVT)	+++	++++	+	++
Nucleus reuniens	−/+	++++	++	−
Hypothalamus				
Anterior hypothalamus	+++//+	+	++	++
ARC	−/+	−	−	−
DMH, anterior part (DMHa)	+++	++	++	++/+++
Posterior hypothalamus	+++++	+++	++	++/+++
PVH	−	++++	−	+++
VMH	++	+	+	−
Medial preoptic area	+++	+++	−/+	+++
AVPV	−	−	−	+++
Lateral preoptic area	+/++	+++	++	+++
Midbrain				
DR	−/+	+++	++	++
Barrington's nucleus	−	++++	−	++/+++
PAG (motor regions)	−+	+++/+	−	−/+
PAG ventrolateral	+++	+++++	++	++/+++
Midbrain reticular nuclues	−	+++/+	−	−
Hindbrain				
NTS, medial part, rostral zone (NTSmr)	−	+++	ND	ND
Parabrachial nucleus	−	+/+++	ND	ND

accumbens (NAc) and other striatal regions; collectively these comprise the mesolimbic DA system [27,80,81]. The finding that the LHA projects to the VTA and NAc therefore suggests that the LHA modulates the DA system to regulate motivated behavior. In this context, we see that the historical classification of the LHA as a "feeding center" does not fully explain its neurophysiologic role. Indeed, the LHA modulates a broad spectrum of motivated behaviors, including the intake of food, as well as drugs, alcohol, water, and general locomotor activity, all via regulation of connected mesolimbic brain areas [54,76–78,82–86]. Thus, perhaps the LHA is better described as a "Motivation Modulation Center", which can coordinate various stimuli with the appropriate mesolimbic regions to execute behavioral outputs.

As our understanding of the LHA has evolved over time, so too has our understanding of motivated behaviors via the mesolimbic DA system. Consumption of palatable food, drugs or participation in sex were initially considered "rewarding" because they promoted DA signaling. Thus, the hypothesis was that DA itself conveyed pleasure, so DA signaling increased hedonia whereas anhedonia resulted if DA signaling decreased [87,79]. This "anhedonia hypothesis" mainly concerned consumption/receipt of rewards, however, and did not explain the noted role for DA in the anticipatory, approach and preparatory aspects of motivated behavior [88]. Berridge and Robinson popularized an alternate hypothesis for reward, in which reward can be broken down into two separable components: liking and wanting [89–92]. "Liking" refers to the subjective appreciation of a stimulus, such as the positive facial expressions produced in infants and rodents in response to sweet tastes (lip licking and tongue protrusions) in contrast to the gapes and disliking facial expressions produced by bitter tastes [91,93]. "Liking" is controlled via opiod, endocannabanoid and GABA-benzodiazepine neurotransmitter systems signaling to "hedonic hotspots" in the NAc shell and ventral pallidum [93–96]. In contrast, a stimulus may be "wanted" even if it is not liked; for example, individuals who take excessive amounts of drugs of abuse (i.e. induce abnormally high DA release) report higher ratings of drug wanting, but no alteration in drug liking [97]. Likewise, rodents with enhanced DA signaling exhibit increased wanting of a sweet reward without actually "liking" it any more than control mice [98]. Wanting thereby imbues a stimulus with *incentive salience*, meaning that the motivation to acquire, approach and consume a stimulus is increased above neutral [92,99]. Wanting/incentive salience is regulated via mesolimbic DA neurons originating in the VTA [89,98,100]. Thus, the LHA (which contains neurons projecting into the NAc/pallidum and VTA) is wired to regulate both the liking and incentive salience components of reward signaling. Any consideration of LHA neurons and their actions (including those regulated by leptin) must therefore consider their role in modulating motivation, and whether they ultimately regulate the liking or incentive salience of stimuli. The remainder of this review will examine the neuronal populations and connectivity of the LHA in this context, and will ultimately address how leptin regulation of the LHA contributes to motivated behavior and energy homeostasis.

4. Getting to know LHA neurons: characterization via neuropeptide content

As suggested by the diverse projection fields of LHA sub-regions, the neurons that make up this area are not homogeneous. The LHA contains both glutamatergic and GABAergic neurons, but expression of these classical neurotransmitters does not fully explain the role of these neurons. The discovery that sub-populations of neurons within the LHA express distinct neuropeptides has considerably advanced our understanding of the individual roles of these populations and the overall role of the LHA in homeostasis and motivated behavior. The following sections will therefore describe the neuropeptide-specific neuronal populations that lie in the LHA, their functions and how leptin regulates these populations to contribute to energy homeostasis and motivated behavior.

4.1. Melanin-concentrating hormone (MCH)

First discovered in the pituitary of teleost fish, melanin-concentrating hormone (MCH) was so named because it regulates skin color changes that are important for background adaption in fish and amphibians. These early studies also suggested that MCH acted via a hypothalamic circuit, since plasma concentrations of MCH varied with environmental stress [101–103]. Indeed, most MCH-expressing cell bodies in mammals are found within in the LHA, as well as minor populations in the DMH and zona incerta [104–106]. The prepro-MCH precursor yields MCH, as well as neuropeptide-E-I (NEI) and neuropeptide G-E (NGE) but the biological significance of these latter peptides remains unclear [106]. In rodents MCH acts via the G-protein coupled MCH receptor (MCHR1), and is expressed in olfaction structures, the DR, VMH, PVN, limbic areas (including the septum and amygdala) and also densely within the NAc shell [107]. Humans and primates also express a second MCH receptor (MCHR2) but its importance in MCH action is not yet known [108]. MCH neurons fall into two sub-populations, those that contain glutamate and a GABAergic population that co-expresses cocaine- and amphetamine-regulated transcript (CART) [109].

MCH has been characterized as an orexigenic neuropeptide that regulates energy homeostasis. MCH action is mediated centrally, where acute treatment promotes food intake in rodents, as well as water intake [110,111]. Chronic treatment with either MCH or an MCHR1 agonist also increases food intake as well as body weight (including white adipose tissue), and mice over-expressing MCH are obese [112–114]. In contrast, mice lacking MCH are lean due to hypophagia and increased metabolism, and exhibit elevated heart rate suggesting increased sympathetic tone [115,116]. MCH neurons polysynaptically project to peripheral targets (including brown adipose tissue) via the NTS, by which they can regulate sympathetic responses that contribute to energy homeostasis [67,86]. Similarly, MCHR1 antagonists reduce food consumption and body weight, as well as improving measures of depression and anxiety. In fact, MCH may have a role in potentiating stress-regulated food intake [116,117]. MCH is also an important regulator of the rewarding responses to drugs and alcohol [77,115,118] which occurs, at least in part, via regulation of the NAc [119,120].

4.2. Hypocretins/orexins

Two groups independently reported another LHA neural population expressing a neuropeptide that they termed as either hypocretin [121] or orexin [122], henceforth referred to as OX. There are two forms of the neuropeptide, OX-A and OX-B, which act via two G-protein coupled receptors (OXR1 and OXR2). While OX-A and OX-B themselves are very similar, they may mediate distinct actions via binding to their receptors. OxR1 is only coupled to G_q proteins and preferentially binds to OX-A. By contrast, OX2 is coupled to $G_{i/o}$ and G_q proteins and binds both OX-A and -B with equal affinity [122,123]. A few cell bodies expressing OX are found in the DMH, but most are located in the perifornical region of the LHA. In contrast to the compact localization of cell bodies, OX projections are widely dispersed throughout the rostral–caudal continuum of the brain. Particularly dense sites of OX innervation include the locus coeruleus, DR, PAG and paraventricular nucleus of the thalamus, structures important for regulation of arousal and sleep. Indeed, OX deficiency in rodents and humans results in narcolepsy, and evidence suggests that OX crucially regulates the transition between sleeping and waking [124–128]. OX neurons also send relays via the hindbrain and spinal cord to regulate the autonomic and sympathetic nervous system [66,67,86,129]. Additionally, OX neurons innervate many regions involved in regulating behavior, including the amygdala,

septal area, medial preoptic area, and substantia innominata as well as the VTA and the NAc, the main components of the mesolimbic DA system [130,131]. OX neurons express the neurotransmitter glutamate and increase the activity of VTA DA neurons that project to the NAc shell [132,133]. OX neurons also express dynorphin and neuronal activity-regulated pentraxin (NARP), which is important for clustering of AMPA receptors and regulation of glutamate signaling [134,135].

Functionally, OX is important in the regulation of sleep, energy homeostasis and motivated behavior. The OX system promotes arousal and may be a therapeutically tractable pathway for treatment of sleep disorders [136]. As such, clinical trials are investigating the efficacy of OX antagonists for treatment of insomnia [137]. The role of OX in energy homeostasis is complex, and it remains unresolved whether OX is truly an orexigenic (appetite enhancing) signal. Acute OX treatment promotes food intake in rats during the light phase (when they do not normally eat), but does not augment food intake during the dark phase (when they normally feed) [122,138,139]. These differences may be attributable to the role of OX in arousal — an animal must be awake to feed, so promoting arousal during the light cycle would increase the overall feeding duration and total intake. OX also regulates DA signaling, suggesting it may have a role in determining the incentive salience of rewards, such as food and drugs of abuse, that may ultimately alter food intake [76,140–143]. Thus, OX could make food intrinsically more wanted, thus promoting increased feeding. Interestingly, the importance of the OX system in regulating motivated behavior varies according to the "reward value" of the stimulus. For example, OX-R antagonists attenuate the incentive salience of cocaine and morphine much more so than energy dense (high fat) food, but do not regulate the incentive salience of low-fat food (chow) [76]. Indeed, mice with disrupted OX signaling do not exhibit increased intake of chow, but changes in OX signaling do regulate the intake of energy dense substances, such as sucrose or high-fat chow [76,144,145]. The OX system also regulates locomotor activity via the mesolimbic DA system, coupling energy status/reward with behavioral response. Acute treatment with OX promotes locomotor activity and OX receptor antagonists attenuate physical activity [142,146,147]. Rodent models of OX deficiency exhibit decreased locomotor activity without a countermanding decrease in food intake, which contributes to the development of obesity in these animals [124,126,148]. OX, therefore, may collectively regulate energy homeostasis via simultaneously regulating awakeness, locomotor activity and promoting hedonic intake.

4.3. Other neuropeptides expressed within the LHA

The LHA has a small population of corticotropin-releasing factor (CRF)-containing neurons, though nowhere near the number that is found in the PVH [149]. CRF has an important role in regulating stress response, and mediates some of these actions via the mesolimbic DA system [150]. Similar to the effects of acute OX treatment, CRF injection into the LHA induces grooming, eating and locomotor activity concomitant with increased heart rate [151]. Indeed, several lines of evidence suggest an interaction between the CRF and OX systems. OX neurons express receptors for CRF and mice lacking CRF receptors exhibit abnormal regulation of OX neurons in response to stress [152]. OX neurons may in turn regulate PVH CRF neurons, but OX predominantly regulates via the VTA while CRF does not. As a result, OX and CRF systems may be co-activated, but are likely mechanistically divergent [153,154].

Neurotensin has been described in the LHA but also in neurons distributed throughout the forebrain, midbrain and in various regions in the hypothalamus, including the ARC, DMH and PMV [155,156]. Central neurotensin is implicated in the sensitivity to pain and temperature, osmotic control, reward signaling, and food intake, though these actions have not been attributed to any particular populations of neurotensin-containing neurons [157–159]. Some LHA neurons containing neurotensin project to the parabrachial region and DR, though the functional significance of these connections remains unclear [160,161].

The LHA also contains a population of neurons that express galanin, and some of these also co-express vasopressin [162]. Galanin injections into the LHA increase food intake in fasted and sated rats through a yet-unclear mechanism. [162]. The related Galanin-like peptide (GALP) also stimulates feeding behavior and may regulate MCH and OX-containing neurons [163,164].

5. The role of leptin action via the LHA

The discovery and characterization of leptin, an anorectic hormone, suggested that it might diametrically regulate the LHA, which had initially been considered as a "feeding center." Fasting (which decreases circulating leptin) and diet-induced obesity (in which neurons no longer respond normally to leptin) increase neuronal activation in the LHA — these data suggested that leptin normally acts to suppress the LHA "feeding center" [165,166]. The evolving understanding of the LHA as a general "motivation modulation area," however, has broadened our scope for leptin action via the LHA beyond feeding alone. For example, intracranial self-stimulation in the LHA (a measure of general reward, not necessarily reward induced by consumption of food or drugs) is also attenuated by leptin treatment [167]. Thus, in order to understand leptin action at the LHA we must consider not only the classical studies concerning food intake effects, but also how motivated behaviors for non-food stimuli may be affected.

5.1. The LHA is an intersection of the energy balance and mesolimbic DA systems: A role for leptin regulation

It is becoming clear that energy status modulates intake of "rewards", such as drugs of abuse or alcohol, suggesting that there must be a link between systems regulating homeostasis and DA-mediated reward signaling. For example, caloric restriction increases the motivated intake of food and drugs, relapse to drug taking, and the amount of work an animal will do to obtain drugs [80,168]. DA is crucial for feeding and locomotor behavior, including the hyperphagia observed in obese leptin-deficient mice [169]. Further, obesity deranges DA-regulated motivated behaviors: diet-induced obese, but not lean rodents, exhibit compulsive-like feeding behaviors that are not altered by aversive stimuli [170]. These effects may even be translated via the maternal environment to offspring — the motivated intake of high-fat food is increased in progeny from obese dams compared to offspring from lean dams [171]. One possible interpretation of these data is that the incentive salience of "reward" stimuli is altered in models of disrupted energy state, thereby promoting increased intake. As such, signals communicating energy status might play a regulatory role in this process, as has been documented for insulin and ghrelin (the appetite-increasing hormone), which regulate the motivated intake of food, drugs and locomotor activity [172–174].

Leptin also regulates DA signaling circuits, and thus could regulate the incentive salience of food and non-food stimuli. For example, leptin treatment of leptin-deficient children diminishes their ratings for food "rewards," and leptin status modifies reward responding in rodents [36,37,167,175–177]. While some leptin-responsive mediobasal neurons innervate the LHA [178] these neurons do not account for leptin regulation of incentivized intake and motivated behavior, indicating that there must be another population of LepRb neurons mediating these effects. Neurons within the LHA, however, directly regulate mesolimbic centers and leptin regulates several LHA neuronal populations, including LepRb neurons within the LHA [133,146,150,179]. Thus, the LHA represents an intersection between

the homeostatic and mesolimbic DA systems and is a likely site by which leptin modulates DA signaling. While the physiologic relevance of leptin-regulated DA changes is yet unclear, the DA system is a crucial regulator of the incentive salience of stimuli. This suggests that leptin could regulate the "wanting" component of reward via regulation of the mesolimbic DA system, though more work is required to definitively explore this hypothesis. Regardless of how this DA signal is ultimately interpreted (wanting, learning, etc.), the LHA is poised to integrate the leptin and mesolimbic DA systems, and so the remainder of this review will therefore address leptin action via known LHA neuronal populations, both in terms of their roles in energy balance and DA signaling.

5.2. Leptin regulation of MCH neurons

The presence of orexigenic MCH neurons within the LHA suggested that these might be targets of anorectic leptin signals. Acute leptin treatment decreases MCH expression [180], and conversely mice deficient in leptin have increased MCH and MCHR1 expression that is reduced by leptin treatment [181–183]. Mice lacking MCH are hypophagic and lean, suggesting that MCH and leptin signals are antagonistic [115]. Indeed, mice double null for MCH and leptin weigh less than mice only null for leptin (*ob*/*ob*). While both lines of mice are similarly hyperphagic, the MCH/leptin null animals have increased energy expenditure and locomotor activity that potentiates weight loss [184]. Thus, MCH may not be as important as an orexigenic factor as it is a suppressor of activity. This is consistent with the finding that MCH reduces neuronal firing in the NAc, where DA acts to promote locomotor activity [120]. Further, MCH neurons project to OX neurons and inhibit their activity [185,186]; since OX regulates mesolimbic DA to promote locomotor activity, this circuitry may further suppress locomotor responses. The increased ambulatory activity in mice lacking MCH may therefore be due, in part, to lifted suppression of OX neurons and increased DA signaling.

5.3. Leptin regulation of OX neurons

Almost immediately after its discovery OX was investigated as a likely regulation point of the anorectic leptin system. Indeed, initial results suggested that leptin acts to suppress OX signaling. Depleting leptin via acute fasting increases OX and OXR1 expression and increases the excitatory synaptic inputs onto OX neurons. By contrast, leptin treatment inhibits OX expression and neuronal activity in normal fed animals, in part by reducing the excitatory inputs onto OX neurons [187–190]. Disruption of appropriate leptin signaling, however, disregulates the OX system: obese rodents with genetically ablated leptin signaling (*ob*/*ob* and *db*/*db* mice, and *fa*/*fa* rats) have reduced OX expression that is restored to normal levels with leptin treatment [191–193]. OX levels in obese humans are also increased by weight loss and restoration of leptin sensitivity [194]. Thus, OX expression itself is not an indicator of appetite; in fact OX over-expression protects animals from diet-induced obesity and the associated decrease in locomotor activity, including reducing food intake. Increased OX expression also potentiates weight loss with leptin treatment [144]. The presence of leptin, however, is crucial for OX action; OX over-expression does not protect leptin-deficient mice from diet-induced obesity [144]. Overall these data suggest that leptin control of OX neurons is complex but required for appropriate energy balance. Less clear is how this leptin regulation of OX neurons affects the mesolimbic DA system, a main output of OX signaling. Given that leptin normalizes both OX expression and the DA system of leptin-deficient animals, it seems likely that leptin might regulate these processes via an integrated system.

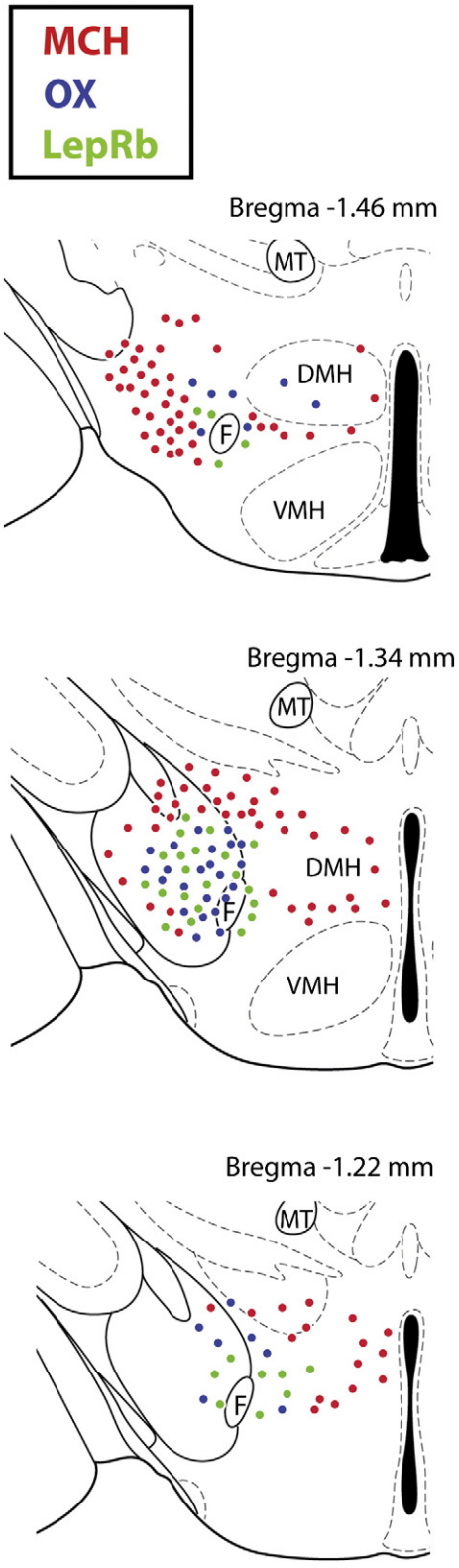

Fig. 1. Distribution of MCH, OX and LepRb neurons in the LHA of the mouse. Levels of the mouse brain according to the stereotaxic atlas of Paxinos and Watson [52]. Only the left hemisphere is shown for each brain level. Red circles = MCH neurons, blue circles = OX neurons, green circles = LepRb neurons. F = Fornix, VMH = ventromedial hypothalamus, DMH = dorsomedial hypothalamus, MT = mammillothalamic tract.

5.4. Leptin action via LepRb neurons in the LHA

In 1998 a large population of LepRb neurons was reported in the LHA [22] but the role of these LHA LepRb neurons is just beginning to be appreciated. LHA LepRb neurons do not co-express MCH or OX and represent a unique population in the LHA. The LHA LepRb neurons are primarily co-distributed amongst the OX neuronal population within the perifornical area, and both populations are surrounded by the MCH-containing neurons (Fig. 1). All LHA LepRb neurons express the inhibitory neurotransmitter GABA, consistent with the hypothesis that anorectic leptin would suppress LHA actions in feeding and behavior. Indeed, leptin administered selectively into the LHA inhibits food intake and promotes weight loss in rats. In addition to regulation of energy homeostasis, LHA LepRb neurons project to and regulate the mesolimbic DA system. Restoring normal leptin levels only in the LHA of leptin-deficient *ob*/*ob* mice increases TH expression in the VTA (which is abnormally blunted) and increases DA content in the NAc. These data suggest that leptin action via the LHA is crucial for normal regulation of the DA system and energy homeostasis [179].

LHA LepRb neurons also regulate neurons within the LHA, and may thus indirectly regulate energy balance and the mesolimbic DA system. In addition to the VTA, LHA LepRb neurons also project onto OX neurons. Leptin treatment increases OX expression in *ob*/*ob* mice through this connection [193]. Intriguingly, some LepRb neurons also project to MCH neurons, but LHA LepRb neurons do not. The population of LepRb neurons that regulate MCH neurons remains to be determined; identification of this circuitry will be an important step in understanding how leptin regulates MCH action.

6. Conclusions

The connectivity of the LHA with autonomic, sympathetic and mesolimbic systems indicates that is more than a “feeding center”, as it was historically described, but rather regulates the range of physiological responses to stimuli (food, drugs, stress, etc.) Despite the increasing evidence that there is more to the LHA than feeding alone, it is still most often described as containing two populations of orexigenic neurons — MCH and OX. Indeed, further understanding of these neuronal populations suggests that their roles are more than merely appetitive. Similarly, the role of leptin via the LHA has, thus far, mainly been considered in terms of effects on food intake and weight. While leptin does regulate energy balance via the LHA, the functional mechanism(s) are not as straightforward as first imagined—i.e., leptin does not just inhibit LHA neurons to reduce feeding. Regulation of OX and the leptin system are directly linked, and both are required for functional energy homeostasis. Collectively, these data suggest that we expand our view of the LHA and not only assess its role in appetite, but also in other mechanisms (such as locomotor activity, incentive salience, and energy expenditure) that contribute to energy homeostasis.

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