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The dynamic regulation of appetitive behavior through lateral hypothalamic Orexin and Melanin Concentrating Hormone expressing cells

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Abstract

The lateral hypothalamic area (LHA) is a heterogeneous brain structure extensively studied for its potent role in regulating energy balance. The anatomical and molecular diversity of the LHA permits the orchestration of responses to energy sensing cues from the brain and periphery. Two of the primary cell populations within the LHA associated with integration of this information are Orexin (ORX) and Melanin Concentrating Hormone (MCH). While both of these non-overlapping populations exhibit orexigenic properties, the activities of these two systems support feeding behavior through contrasting mechanisms. We describe the anatomical and functional properties as well as interaction with other neuropeptides and brain reward and hedonic systems. Specific outputs relating to arousal, food seeking, feeding, and metabolism are coordinated through these mechanisms. We then discuss how both the ORX and MCH systems harmonize in a divergent yet overall cooperative manner to orchestrate feeding behavior through transitions between various appetitive states, and thus offer novel insights into LHA allostatic control of appetite.

1. Introduction

The regulation of energy intake is critical to survival and requires coordination between the peripheral and central nervous system. As such, a complex interplay exists between regulatory mechanisms in order to mediate appropriate feeding-related behaviors. Typically, these regulatory mechanisms influence energy balance by coordinating feeding behaviors depending on perceived needs, which requires *transitioning* to relevant behavioral states while suppressing the performance of unnecessary inapposite actions. However, these mechanisms are susceptible to dysfunction as homeostatic regulation is vulnerable to biological and environmental factors that influence energy balance. For example, factors arising from an obesogenic environment (e.g., excess consumption of energy-dense hedonic foods) may dampen homeostatic regulation, such that regulatory pathways that normally

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control energy intake are incapable of defending the body against excess energy storage [1–3]. In the absence of increased expenditure, this leads to weight gain, obesity, and associated comorbidities. In this review, we discuss the role of the lateral hypothalamic area (LHA) as a critical site in the central nervous system (CNS) that integrates both internal homeostatic controls as well as input from environmental and motivational signals to mediate behavioral choices as they relate to the procurement, intake, and metabolism of food.

Early studies on the LHA demonstrated that electrical stimulation of this region profoundly increased food consumption, whereas LHA disruption resulted in dramatic under-consumption of food [4, 5]. Therefore, the LHA was initially characterized as a “feeding hotspot”. However, in addition to influencing energy intake, stimulation to this region also invigorated other motivated behaviors such as drinking, physical activity, and copulation [6, 7]. More recent studies have shown that the LHA expresses a wide variety of molecularly distinct cells that function to coordinate a vast array of motivated behaviors. Within the LHA, Orexin/hypocretin (ORX) and Melanin Concentrating Hormone (MCH) neurons play an important role in driving procurement and ingestion of food: In what follows, we describe the distribution and activity of these populations of LHA neurons and examine how they function to independently and cooperatively mediate the range of behavioral state transitions necessary for energy regulation.

2. Characterization of ORX and MCH neurons in LHA

The lateral hypothalamic area (LHA) is a large diencephalic structure that encompasses close to 50% of the hypothalamus and houses a complex interconnected circuit, in which each cell averages approximately >16,000 synapses [8]. While studies continue to elucidate the molecular diversity of the LHA, within this region, ORX and MCH expressing cells display a similar distribution and project to numerous analogous CNS targets; however, despite this, these two orexigens drive distinct appetitive behaviors.

2.1 Anatomy of LHA

The LHA spans the entire rostral-caudal extent of the hypothalamus—it is an extensive and heterogeneous area, complexly interconnected with mediobasal hypothalamic nuclei including the ventromedial (VMH), ventral premammillary (PMV) and arcuate nucleus (ARC). The LHA emerges anterior to the ventral mesencephalon and is positioned posterior to the preoptic area, though its demarcation is complicated by the lack of a discernable boundary. In the hypothalamus, the LHA borders lateral to the dorsomedial hypothalamus (DMH) and paraventricular nucleus (PVN) and dorsal to the PMV and VMH, and can be divided into rostral (tuberal) and posterior portions [13]. The LHA is ventral to the zona incerta (ZI) and lateral to the mediothalamic tract. The subregion that adjoins the fornix is known as the perifornical hypothalamic area and is located within the ventromedial extent of the LHA. The LHA is ideally located to integrate physiological, gastrointestinal, and sympathetic peripheral signals - such as those relayed from the ARC - with forebrain and mesencephalic motivation and reward signals (for reviews, see [14–16]). Within the LHA, two of the most well characterized neuronal populations are ORX and MCH (Figure 1), which have been shown to influence arousal, energy balance and goal-directed behavior.

2.2 Distribution of ORX and MCH neurons within the LHA

MCH cells were the first population determined to be predominantly located within the ZI and LHA. MCH neurons are widely dispersed in the dorsolateral LHA extending in an anterior to posterior manner where they terminate medial to the subthalamic nucleus. Additionally, a more moderate number of MCH cells are located medial to the internal capsule, whereas a smaller proportion of neurons are located in the perifornical area [18, 24]. ORX expressing cells are located in the DMH and also throughout the LHA, though they exhibit specifically dense concentrations in the perifornical area and the magnocellular nucleus [19, 20]. A small number of cells have been also been revealed in posterior regions of the hypothalamus and subincertal nucleus that demarcates the border between the hypothalamus and thalamus [47]. Thus, both MCH and ORX cells are located in many of the same subdivisions of the LHA, however while both types of cells equivalently populate the LHA [9] and can be intermingled within it, they are non-overlapping (Figure 1).

2.3 Connectivity of LHA ORX and MCH cells

MCH cells receive input from first order feeding neurons originating from the ARC. This includes projections from orexigenic Neuropeptide Y (NPY) as well as Agouti-related peptide (AGRP) neurons. The influence of these orexigenic first order neurons are complex. For example, NPY peptide exerts an inhibitory influence on MCH cells in LHA [21] while administration of MCH peptide increases NPY in hypothalamic section in vitro [22]. These findings suggest that NPY and MCH regulate one another's activity to coordinate food intake. Unlike NPY, intracerebroventricular (ICV) administration of AGRP peptide enhances LHA MCH mRNA [23]. MCH neurons also receive projections from anorexigenic signals such as α-melanin-stimulating hormone (α-MSH) [17, 19]. Thus, LHA MCH neurons interact with first-order feeding signals in the ARC to coordinate food intake.

MCH has its actions by binding to its receptors, MCH-1R and MCH-2R. Notably however, MCH-2R is either absent or functionally inactive in rodents. MCH-1R is expressed throughout the brain, including cerebral cortex, striatum, hippocampus, amygdala and numerous mesencephalic and rhombencephalic regions [18, 24, 25] (Figure 2). In respect to the regulation of appetite control, MCH-1R expression in the ventral striatal nucleus accumbens shell (ACBs) has been demonstrated to be both necessary and sufficient for food intake [26, 27]. In addition, activation of LHA MCH cells increases dopamine turnover in the ventral striatum, which is thought to encode the nutrient and reward value of sugars [28]. The projection patterns of MCH cells can be distinguished based on co-expression of other molecules, such that the vast majority of efferents to forebrain targets also express both neurokinin 3 and CART [29]. MCH cells also project to other areas important for the regulation of food intake such as PVN [30] and parabrachial nucleus [31]. Furthermore, MCH neurons project to myelencephalic targets that coordinate orofacial movements and mastication, including dorsal motor vagus, facial and hypoglossal nuclei [32]. Additionally, through polysynaptic connections to the hindbrain and spinal cord, MCH neurons also regulate brown adipose tissue (BAT) and influence basal metabolic rate and thermogenesis [33–35]. Conversely, MCH LHA cells display few projections to areas on the CNS that regulate arousal such as the locus coeruleus (LC) and periaqueductal gray (PAG) [36–38].

ORX cells also receive neuronal afferents from the ARC, including from NPY, AGRP and α-MSH cells [17, 19, 39]. In LHA slices NPY also inhibits ORX activity [40], which is unexpected considering both of these neuropeptides evoke feeding. ORX ligands are synthesized into two forms, ORX-A and ORX-B, of which ORX-A shows a tenfold higher affinity for the orexin receptor OxR1, whereas both ligands show similar affinity to the orexin receptor OxR2 [20, 41]. Both OxR1 and OxR2 are expressed in the amygdala, bed nucleus of the stria terminalis (BNST) and ventral tegmental area (VTA). However, only OxR1 is expressed in the medial prefrontal cortex (mPFC) and the hippocampus (HPC), while OxR2 is also expressed in hypothalamic regions such as the ARC and PVN. Orexin neurons drive feeding behavior through their hypothalamic innervations including to the ARC, PVN and DMH [42, 43], as well as the VTA [44] and mPFC [45] to attenuate post-ingestive inhibitory feedback [46] and promote cue-evoked overeating behaviors [1], respectively. Moreover, ORX cells in LHA project to numerous regions that modulate arousal such as the LC, PAG and septal nuclei [47, 48]. Finally, through polysynaptic brainstem projections, LHA ORX cells can regulate BAT [49], and white adipose tissue (WAT), and also influence activity of the gastrointestinal system [50], pancreas and liver [51–53].

To date, it remains to be determined whether subpopulations of LHA MCH and ORX cells preferentially project to specific target regions to influence behavior mediated by the release of their respective peptides [10–12]. We suggest that a combination of influences over their projection targets together with the inherent properties of these LHA neuropeptide expressing cells endows them with the capacity to flexibly mediate a broad appetitive behavioral sequence (Figure 3). That is, we propose ORX plays a critical role in coordinating preparatory responses relevant to acquiring food, whereas MCH orchestrates consummatory behaviors more vital to prolonging food intake and the metabolism of food. This coordinated action is posited to take place via interactions with energetic signals (e.g., glucose), as well as reward and hedonic pathways in the brain (e.g., mesostriatal dopamine).

3. ORX and MCH cells display distinct electrophysiological, molecular and synaptic properties

Although both ORX and MCH exhibit orexigenic properties, in many situations the actions of these two populations of cells are different or even opposing. For instance, MCH cells fire under conditions of paradoxical sleep [54] and drive energy conservation [55–57], whereas ORX neurons have been attributed to invigorating wakefulness [42] and promoting energy expenditure [58]. Differences in the biomolecular properties of these classes of LHA cells may underlie their capacity to appropriately switch between vastly different motivational states.

3.1 Electrophysiological and molecular characteristics of ORX and MCH cells

On binding to OxR1, ORX activates Gs and Gq pathways, activity of which includes triggering intracellular IP3 and DAG cascades, resulting in activation of protein kinase C and Ca2+ signaling and culminating in membrane depolarization [43, 59, 60]. OxR2 signaling is also mediated through Gi/o signaling cascades, which opens K+ channels and inhibits

adenylyl cyclase activity to reduces synthesis of cAMP and corresponding cell activity [60–63]. At the same time, both OxR1 and OxR2 are capable of suppressing G-protein regulated inward rectifier channel (GIRK) signaling that typically hyperpolarize and decrease neuronal excitability [64, 65]. Accordingly, the overall result of ORX activity reflects an attenuation of K+ conductance [66–68] and triggering of Na+/Ca2+ exchange currents [43, 59] leading to net excitatory effects of both OxR1 and OxR2 on neuronal activity [60]. MCH binds to MCH-1R activating Gi/o and Gq pathways, triggering a range of downstream effects. This includes enhanced intracellular Ca2+ through IP3 synthesis, reductions in forskolin-mediated elevations in cAMP, and activation of MAPK [25, 69, 70]. Furthermore, in contrast to OxR2, MCH-1R activation has been shown to evoke strong GIRK current [71]. Due in part to this broad competitive intracellular action, cellular effects following MCH-1R activation can be either excitatory (e.g., through the increase in Ca2+), or inhibitory (e.g., by triggering GIRK currents) [37, 69].

Relative to MCH, ORX neurons demonstrate a slightly depolarized resting membrane potential [72]. ORX cells also exhibit spontaneous intrinsic activity by rhythmically generating action potential, whereas MCH containing neurons usually exhibit low activity with few to no spikes at rest [72,73]. Accordingly, MCH neurons are slightly more hyperpolarized than ORX cells recorded under similar physiological conditions and require activation or disinhibition from synapsing cells in order to fire. When stimulated, the vast majority of ORX cells co-release glutamate as well as other regulatory and neurotransmitter signals including Neuronal Pentraxin (NARP) and dynorphin [83]. The co-release of dynorphin in these cells may act in a negative feedback mechanism, dampening the activation of ORX neurons [84]. Conversely, ORX cells can also function in a positive feedback manner, whereby OxR2 activity can itself promote ORX signaling, which may maintain activity of these cells for a prolonged period of time. Transcriptional profiling studies further reveal that almost all ORX containing neurons co-express the protein coding gene implicated in metabolic regulation of nesfastin-1 (NUCB2**)**, the endogenous opioid peptide proenkephalin (PENK) as well as the opioid polypeptide hormone, prodynorphin (PYDN) [85]. Furthermore, ORX neurons express receptors for GABA, glucocorticoids, NPY, melanocortins and leptin [86]. The vast majority of MCH cells also co-express glutamate [87] and vesicular glutamate transporters vGLUT1 and vGLUT2 [86]. A smaller proportion release GABA [88] and contain glutamate decarboxylases, GAD65 and GAD67 [65], the rate limiting enzymes for synthesis of GABA from glutamate. However, MCH neurons do not overlap with vGAT-expressing cells in the LHA, nor do they produce the vesicular transporters vGAT or vMAT [87] that are typically necessary for the synthesis and release of GABA; therefore, the mechanism controlling GABA release via MCH is as yet unknown. MCH neurons also co-release other peptidergic signals including CART, galanin, and nesfatin, and express receptors for GABA glucocorticoids, NPY, melanocortins, and leptin [85,86,90]. In addition to synaptic communication, MCH neurons can influence volume transmission [91], a phenomenon in which peptide release into the extracellular fluid can broadly affect CNS activity via transmission through the ventricles [92].

Interestingly, ORX and MCH containing neurons reciprocally synapse in the LHA and thus can mediate the activity of each other [74]. In slice preparation, application of ORX peptide

evokes sustained membrane depolarization and increases spike frequency of MCH cells by elevating glutamate release [21]. However, this activation occurs only in a subpopulation (≈30%) of MCH cells, whereas the remainder are either unaffected or inhibited by ORX peptide administration [75]. The inhibitory influence of ORX over MCH cells reflects increased GABAergic tone, perhaps via local circuit control of GAD65 expressing cells. Additionally, MCH peptide can inhibit ORX neuronal activity, though this occurs only when ORX cells are highly active (i.e., via activity-dependent inhibition) [77]. An additional mechanism in which these signals could be controlled is through network electrical oscillations [76]. At lower oscillation frequencies (<10 Hz), ORX cells show a proclivity for stimulation [78]. Conversely, high frequency gamma oscillations (30–200 Hz) specifically silence ORX cells, while promoting activity in MCH neurons [78]. Thus, reciprocal inhibitory signaling [75, 77] and frequency-dependent modulation [78–80] could enable fast switching between different physiological and behavioral states that are respectively controlled by ORX and MCH cells.

3.2 ORX and MCH responses to energy status

The control of blood glucose is vital for regulating the energy status of an organism and is determined in part by glucose-sensing cells in the hypothalamus [93]. ORX cells are stimulated in response to hypoglycemia, including when evoked by insulin treatment [94–97], and promote glucose utilization under fasted but not *ad-libitum* testing conditions [98]. Consistent with the reduced activity of the ORX system in response to energy surfeit, approximately 50% of ORX cells are hyperpolarized when glucose levels are high [94, 97, 99]. On the other hand, MCH neurons are excited in response to glucose [99, 100] and are necessary for mediating the metabolic value of sugars [28]. However, this latter finding may reflect the co-release of other neurotransmitter or peptide signals as MCH-1R deletion does not influence glucose-conditioned flavor preferences [223].

In the periphery, the major pre-prandial signal controlling meal initiation is ghrelin, a 28-amino acid peptide that is secreted from gastric mucosa cells in the stomach. Ghrelin works by binding to its receptor, growth hormone secretagogue receptor (GHSR). When binding to GHSR, ghrelin undergoes posttranslational octanoylation via the membrane bound enzyme, ghrelin O-acyltransferase (GOAT) [103, 104]. Two receptor subtypes have been identified – GHS-R type 1a, which is a G-protein coupled receptor, the activation of which leads to phosphorylation and N-linked glycosylation [105, 106]: and GHS-R type 1b, a pharmacologically inert and truncated form of the type 1a receptor [105, 107, 108]. Ghrelin is thought to influence hypothalamic activity either directly via the fenestrated capillaries of the median eminence [109], or indirectly through vagal afferents [110]. Bath application of ghrelin enhances ORX cell firing [97] and influences glucose sensitivity in ORX cells [94], whereas ICV ghrelin infusion leads to an increase in the marker for neuronal activity, FOS (protein product of *c-fos* gene), in ORX but not MCH cells [111, 112]. Moreover, ghrelin-evoked feeding is dependent upon intact orexin signaling in the LHA [113, 114]. By contrast, ICV ghrelin is still able to evoke food intake in MCH-1R KO mice. Thus, ghrelin-ORX but not MCH interactions appear critical for regulating appetite.

Peripheral satiety signals also differentially influence the ORX and MCH systems. Cholecystokinin (CCK) is secreted in response to nutrients in the intestinal lumen [116, 117] where it delays gastric emptying and inhibits food intake. Vagal afferent neurons are targeted by peripheral signals for the modulatory control of food intake and ORX administration can inhibit the influence of CCK on these neurons [118]. CCK activates ORX cells via the CCK-A receptor [119], whereas it has been shown to directly downregulate MCH-1R on vagal afferent neurons [118] and inhibit MCH release [120–123]. The pancreatic peptide amylin and its receptor salmon calcitonin (sCT) have an inhibitory influence over the LHA; however, while both amylin and sCT decrease mRNA expression of ORX, only sCT reduced expression of MCH mRNA [124]. Finally, the adipokine leptin is synthesized in response to the proportion of body fat and signals energy surfeit. In the LHA, leptin exerts its influence via the receptor, LepRb, which several studies suggest synapses with ORX but not MCH cells [16, 125, 126,127]. Pretreatment with leptin can partially block ORX-A and -B evoked feeding. However, findings are mixed with respect to the mechanism of action of LepRb on ORX cells. That is, while immunoreactivity for LepRb has been noted in ORX cells [128, 129], the antisera used in these studies binds both to the long signaling form of LepRb, as well as its short non-signaling isoform. Furthermore, using genomic approaches that specifically label LepRb-expressing neurons, ORX cells appear not to express LepRb nor are they directly regulated via leptin [127, 130]. By contrast, LepRb is expressed in MCH neurons and may indirectly inhibit MCH activity via disrupting endocannabinoid signaling [86, 131]. Interestingly, the increased adiposity resulting from leptin depletion is rescued in mice deficient in MCH. However, while a drastic reduction in body weight relative to ob/ob mice was revealed, deletion of MCH did not attenuate hyperphagia, but rather reflected a striking increase in energy expenditure.

3.3 ORX and MCH interactions with mesostriatal reward circuitry

Reward circuitry in the brain plays a fundamental role underlying the motivational and hedonic components of food intake and under certain circumstances promoting excess energy intake independent of metabolic need. Dopamine (DA) cells in the VTA are believed to play a particularly important role in modulating reward learning and motivation. In the LHA, ORX cells project to the VTA [47, 132–134] and are known to facilitate DA signaling [135]. Application of ORX-A onto VTA DA cells leads to an increase in NMDAR-mediated synaptic transmission [136] and underlies projection-specific targeting to mesostriatal targets [137]. Moreover, 24 hr fast results in an increase in NMDAR current amplitude in VTA DA cells, which can be blocked by bath application of OxR1 antagonist [95]. Ghrelin can also promote DA signaling in VTA, however these effects are dependent on OxR1 signaling, which suggests a critical role for ORX cells in mediating interactions between ghrelin and DA signaling [114, 138]. When administered into VTA, ORX-A enhances meal size by suppressing post-ingestive negative feedback resulting from palatable food consumption [44]. While OxR1 and OxR2 receptors are expressed in VTA [139–141], the nature of ORX modulation remains debated as the vast majority of LHA ORX fibers project though the VTA with only a small proportion synapsing directly onto cells within this region [142]. This latter finding suggests that modulation via ORX may be volumetric in nature [143, 144]. Interestingly, DA can also directly modulate ORX activity within the LHA in a bidirectional manner, such that low and high concentrations of DA, respectively increase and

decrease activity of LHA ORX cells [145]. The ACBs in the ventral striatum is a major target of mesencephalic DA and plays a critical role as an interface between feeding and reward [146]. OxR2 is densely expressed in ACBs [147] and administration of ORX into this region stimulates food intake [148, 149] in part via heightening the hedonic value of food [150].

MCH activity within the VTA is complex and not clearly defined. Earlier studies suggested cell projections from LHA to VTA displayed moderate expression of MCH-1R mRNA and immunoreactive fibers [32, 151]. However, in a transgenic knock-in mouse model, no detectable MCH-1R expression in VTA was noted [152]. Consistent with the latter findings, application of MCH to VTA neurons was shown to have no effect on their activity. With respect to the ACBs, dense LHA MCH innervations have been noted [18] and administration of MCH into this region drives feeding behaviors [26]. Moreover, MCH is required for ventral striatal DA release that typically proceeds sucrose ingestion and reflects the rewarding value of sucrose metabolism [28]. LHA MCH cells that project to ACBs co-express CART [29], which is noteworthy as CART-immunoreactive neurons in ACBs encode drug-associated cues [222]. This may indicate that LHA MCH-CART projections to ACBs encode conditioning and environmental cues associated with reward. MCH-1R is expressed on both D1 and D2 medium spiny neurons (MSNs) where it acts in an inhibitory manner by increasing K+ conductance through Gi/o signaling [27]. Through this mechanism, MCH may inhibit ACBs MSNs to promote ingestive behavior. Moreover, MCH itself can display an antagonistic role on DA signaling in this region, by reducing DARRP-32 phosphorylation [27]. Conversely, it has also been reported that MCH and DA may collectively enhance ACBs firing [220]. While the nature of these discrepant findings requires further characterization, they may reflect different Gq or Gi proteins with which activation of MCH-1R is capable of triggering. Finally, a recent study [222] revealed that selective activation of LHA-MCH neuronal projections to ACBs promoted feeding in male but not female rats. In addition, ovariectomized females treated with vehicle (but not estradiol) displayed increases in food intake upon MCH administration into ACBs. These findings indicate that LHA MCH projections to ACBs may serve as a critical target site for mediating the sex differentiated effects of MCH-dependent feeding behavior [222].

4.0 ORX and MCH modulation of food-seeking and intake

The nuanced properties discussed above position ORX and MCH cells to support an array of orexigenic behaviors necessary for the consumption of food, many of which are functionally distinct. Food-seeking, for example, requires the active procurement of food and expends energy, whereas consumption requires an animal to appropriately terminate food-seeking in order to engage in the act of eating itself. Interactions between ORX and MCH may provide the LHA with the capacity to modulate arousal, food-seeking, and consumption to invigorate energy intake.

4.1 Arousal

Stimulation of the ORX system through either pharmacological or genetic means enhances wakefulness and arousal, whereas it decreases REM sleep [153–155]. Conversely, a loss of

ORX neurons greatly augments REM sleep [156] and hypoactivity is noted in response to ORX cell ablation [97]. ORX stimulation also enhances energy expenditure [58] and disruptions in ORX signaling leads to reduced energy expenditure due to decreased locomotor activity [157]. Recently, ORX cell activity has also been shown to predict self-initiated movements [158]. In contrast to ORX, MCH promotes REM sleep [54] and much like MCH gene deletion in ob/ob mice, MCH cell inactivation results in hyperactivity [159, 160] suggesting LHA MCH cells are typically involved in the suppression of locomotion. Moreover, the classical neurotransmitters of the arousal system—noradrenaline and acetylcholine—stimulate ORX but silence MCH activity [161].

4.2 Food anticipation and seeking

In order to survive an organism must successfully forage in their environment, which requires careful selection among a range of complex behaviors and the capacity to anticipate when food will be available. Typically, animals display an increase in locomotor activity in the period preceding predictable food availability [162]. This food-anticipatory activity (FAA) is under the control of a food-entrainable oscillator, a speculated molecular timekeeping mechanism which integrates information of predictable food [163–165]. ORX cells display enhanced FOS activity during FAA [166, 167], whereas neuronal ablation significantly impairs this phenomenon [166]. Although the brain systems underlying FAA remain to be elucidated, it is possible that interactions of ORX neurons with cholinergic and monoaminergic circuitry [168] and LHA ORX projections to the tuberomammillary nucleus [47] underlie ORX modulation of FAA. Conversely, although MCH-1R deletion generally increases locomotor activity during the dark cycle, the MCH system is not required for FAA [169].

In addition to anticipating its availability, animals must also successfully acquire food to assure that their needs for survival are met. In this regard, the effects of ORX can be dependent on the motivational status of the animal—a critical variable when considering whether to engage in food acquisition. Thus, under conditions of food restriction but not free feeding, peripheral treatment with an OxR1 antagonist in rats disrupted operant responding for sucrose under fixed ratio, progressive ratio, as well as cue-induced reinstatement testing conditions [170]. While these results are consistent with electrophysiological findings in which fasting enhances ORX expression [97, 171], food deprivation is not always necessary for ORX modulation of food-seeking. In rats, third ventricle infusion of ORX-A increased progressive ratio responding for sucrose pellets, whereas systemic blockade of OxR1 disrupted performance in this task [172]. The projection targets from that underlie this influence over sucrose responding are unknown, but likely reflect broad interactions of LHA ORX cells with reward circuitry including basal forebrain circuitry and mesencephalic DA [170]. In addition, fourth ventricle infusions of ORX-A also enhanced progressive ratio responding, implicating a role for hindbrain ORX signaling in mediating food-seeking behavior [173]. Given that ORX-1R and immunoreactive ORX-A fibers are noted in the brain stem [47, 174], LHA ORX cell projections to these downstream targets may underlie the influence of ORX on motivated food-seeking [173]. MCH appears to play a less meaningful role in food-seeking as deletion of MCH-1R has no effect on operant responding for sucrose [175, 176]. Similarly, pharmacological blockade of MCH in dorsal hippocampus

was found to be without effect on food-seeking in a spatial working memory task [177]. Furthermore, deletion of MCH-1R or systemic treatment with an MCH-1R antagonist does not influence the capacity of a sucrose-paired conditioned stimulus (CS) to augment ongoing operant performance (i.e., Pavlovian-instrumental transfer) [175]. MCH-1R deletion has however been shown to enhance responding under progressive ratio testing conditions [176], suggesting that unlike ORX, the MCH system may generally serve to attenuate this form of incentive-based responding.

Further distinctions between ORX and MCH on their influence over food acquisition are revealed when one considers the nature of the reward being acquired. As mentioned above, ORX effects on sucrose self-administration are mostly observed when animals are tested in a food deprived state [170]. However, when the non-nutritive sweetener saccharin is used as a reinforcer, OxR1 antagonism disrupts operant responding and cue-induced reinstatement regardless of deprivation state [178]. This effect of operant responding for rewards independent of caloric value stands in direct contrast to treatment with the MCH1-R antagonist GW803430, which disrupted sucrose but not saccharin responding. This indicates that the caloric and colligative properties of a food are necessary to any limited role for MCH in acquiring food [179]. This latter finding is in contrast to the effects of targeted deletion of MCH-1R, which leaves intact glucose-conditioned flavor preferences [223]. The basis for this discrepancy might reflect the nature of the disruption in MCH-1R signaling (i.e., congenital ablations, pharmacological blockade), paradigm (i.e., Pavlovian flavor preference, operant responding) or species (mice, rats). Finally, additional differences between ORX and MCH on food seeking have been noted in tests of impulsivity and behavioral inhibition. While systemic antagonism of OxR1 leads to suppressed motivation to engage in a stop-signal reaction time task, it does not influence response inhibition, indicating the ORX system is not important for impulse control [180]. However, LHA MCH containing neurons may mediate response inhibition through descending projections to the ventral hippocampus (vHPC), a region implicated in behavioral impulsivity [181]. Indeed, both pharmacological administration of MCH peptide to the vHPC, as well as selective activation of LHA MCH neuronal projections to this region, increase behavioral impulsivity in a differential reinforcement of low rates of responding task. Interestingly, RNA interference of MCH expression in this pathway also increased behavioral impulsivity, indicating that both increases and decreases in MCH signaling affect impulsivity. Notably, stimulation of MCH signaling did not affect either progressive ratio responding nor interval timing, indicating a selective role for MCH neurons that project to the vHPC in regulating impulsivity [182].

4.3 Consumption of food

Given their labels as orexigens, it is not surprising that ICV administration of either ORX [183, 184] or MCH [185, 186] promotes food intake, whereas systemic pharmacological blockade of their respective receptors leads to intake inhibition [179, 187]. Chemogenetic stimulation of ORX also evokes feeding behavior, and conversely extensive (but not moderate) neuronal ablation attenuates intake of lab chow [188]. Fourth ventricular infusions of ORX-A enhances chow consumption by increasing meal size [189, 190] and this effect is dependent upon intact catecholamine signaling within the hindbrain [189, 191].

In contrast, hindbrain infusions of MCH failed to evoke an orexigenic response for sucrose or saccharin [192] thus, unlike ORX, MCH evoked feeding appears to selectively require forebrain stimulation. Within the LHA, injections of ORX or MCH promotes food intake in a dose-dependent manner [183, 193, 194].

Both ORX and MCH have also been shown to play an important role in learned overeating behaviors, in which a CS can influence eating behavior independent of metabolic need (i.e. cue-potentiated feeding; CPF) [1]. Orexin signaling in the medial prefrontal cortex (mPFC) is implicated in the expression of CPF as systemic blockade of OxR1 prevents both CPF and the expected increase in FOS induction in the mPFC [195]. In addition, targeted mPFC blockade of OxR1 also prevented CPF in sated rats [45]. These findings indicate that projections from LHA ORX cells to mPFC underlie CS evoked feeding responses. Similarly, CPF also appears to require intact MCH-1R signaling [196]. However, when a CS that had been shown to invigorate CPF was presented in the absence of food, it selectively induced FOS activity in LHA ORX but not MCH cells [197].

While the above findings suggest that prolonged activation or long-term disruption of ORX and MCH can broadly influence food intake, when more subtle observations are carried out, the influence of these orexigens on feeding behavior can be readily distinguished from one another. Using in-vivo Ca2+ imaging, Gonzalez et al., recorded dynamic changes in ORX cell activity to reveal a surprising rapid attenuation in cell activity as mice engaged in eating behaviors. This silencing in ORX activity quickly rebound once mice discontinued food consumption [198]. Thus, when dynamic changes in ORX cell activity are tracked, the putative firing rate of these cells becomes weaker as animals engage in food intake. Similar findings were reported using juxtacellular labelling procedures, where ORX cells fired in response to the presentation of an auditory CS associated with subsequent delivery of a sucrose solution. This enhanced firing rate quickly dissipated upon the initiation of licking [199]. By contrast, if acute optogenetic stimulation of LHA MCH cells is timed to coincide with the consumption of food, increased intake is observed [200]. Furthermore, during the consumption of food the activity of MCH neurons communicates nutrient value to provide post-ingestive reward feedback, such that optogenetic stimulation of MCH neurons during consumption of non-caloric sucralose inverts an innate preference for sucrose [28]. This suggests that the pairing of MCH stimulation with sucralose consumption retrieves the positive post-ingestive values associated with nutritive sweeteners such as sucrose. In the same model, stimulation of MCH neurons increases striatal dopamine release in a manner that coincides with the type of post-ingestive reward signaling attributed to dopamine neurons [201]. Interestingly however, optogenetic stimulation of LHA MCH cells does not alone initiate food intake [200], further aligning with the idea that ORX and MCH play distinct roles in the procurement and consumption, respectively, of food.

5.0 Dynamic orchestration of appetitive behaviors via LHA ORX-MCH interactions

We suggest that the ORX system plays an integral role in setting the stage for searching, acquiring, and anticipating the delivery of food. Manipulations of this orexigen robustly

influence these preparatory behaviors, which indirectly impact the likelihood that an animal engages in the consumption of food. Alternatively, MCH plays a less prominent role in behaviors that are more distal to food delivery, though it has a direct and far-reaching influence on consummatory behaviors at later stages of the appetitive behavioral sequence (Figure 3).

5.1. From food-seeking to intake: Transitions from LHA ORX to MCH cell activity

Both ORX and MCH neurons in the LHA play a multifaceted role in a range of motivated behaviors including sleep, arousal, maternal caregiving and appetite control [14, 89, 202]. It is unlikely that the same population of cells underlie control of these distinct motivated behaviors. Thus, we suggest that glucose-sensing ORX and MCH cells in particular function to mediate behavioral transitions from seeking to consumption. In this regard, the low glucose levels that accompany hunger could serve to directly stimulate activity in LHA ORX glucose-sensing cells [94–97], which is mediated by activity of the peripheral hunger signal ghrelin [94]. Activity of LHA ORX cells would be expected to facilitate responding to environmental cues predictive of food via projections to mPFC [45]. Moreover, given that ghrelin facilitates phasic firing of DA cells in VTA, which requires OxR1 signaling [114,138], these ghrelin-ORX interactions could enhance DA synthesis and activation of the mesostriatal pathway that is critical for reward-based responding [47, 132–138, 172, 203]. When searching out food it is also advantageous that competing behaviors involved in direct consummatory acts be suppressed. With this in mind, optical activation of LHA ORX cells can inhibit MCH cells via ORX mediated increases in GABAergic signaling [21]. Moreover, ghrelin does not influence MCH [111, 112] and unlike ORX, MCH signaling is not necessary for ghrelin-initiated feeding [115]. Additionally, the DA release resulting directly from ghrelin [204] and/or ORX [47, 132] might also serve to dampen MCH activity [205].

Once food has been acquired, we suggest that a rapid flexible transition from ORX to MCH activity is required, which could be driven by several potential mechanisms (Figure 4). First, MCH can exert an inhibitory influence over ORX in an activity-dependent manner [77]. Thus, when ORX activity is elevated, inhibition via MCH could be critical in allowing for fine-tuning between these two classes of cells. It is also perhaps worthwhile considering that ORX cell activity is greatest immediately prior to contact with food [199]; therefore, MCH would be expected to have its strongest inhibitory influence over ORX at the time when behavioral state transitions (i.e., seeking → feeding) are imminent. Second, descending high frequency gamma oscillations originating in the lateral septum may also have the capacity to flexibly modulate transitions from ORX to MCH activity [78]. Third, it is well known that the endocannabinoid system functions as a pre-synaptic mediator for the release of neuropeptides and neurotransmitters [206]. Activation of the cannabinoid type-1 receptor (CB1) induces a rapid transient though significant suppression of ORX activity. At the same time, CB1-activation also depolarizes MCH cells via presynaptic attenuation of locally synapsing GABAergic neurons [207]. It would be interesting to examine if these are the same population of cells that are proposed to mediate increased ORX-dependent GABAergic drive onto MCH [75]. These effects may underlie the well-documented role of the endocannabinoid system on food intake in general [208], and influence rapid ORX to MCH transitions in particular. Forth, the rising levels of glucose that accompany the metabolism of

food serve to inhibit ORX and stimulate MCH cells [99, 100]. Finally, any inhibition to ORX cell activity could disrupt ORX-dependent GABAergic drive onto LHA MCH cells; thus, further disinhibiting them [75]. Collectively, as animals engage in the consumption of food, this ORX to MCH transition in neuronal activity would promote the rewarding post-ingestive [28] and hedonic value of sugars [196, 209] resulting in the maintenance and prolonging of food intake [200].

5.2 Disruptions to LHA ORX and MCH activity in dietary obesity

Dietary obesity leads to profound changes in physiology with both ORX and MCH displaying many divergent structural and functional alterations. On initial exposure to a high-fat diet, ORX cells displays an increase in spontaneous miniature excitatory post-synaptic current (mEPSC) amplitude immediately upon the animal gaining access to a high-fat diet [210]. This would be expected to augment ORX-dependent appetitive behaviors, including an increase in food anticipatory behaviors [166] and cue-potentiated feeding [45]. Food cues in the environment can promote eating independent of metabolic need, which is thought to contribute to weight gain and obesity [211]. Thus, under this early period of high fat diet exposure, the heightened activity of the ORX system would be expected to enhance vulnerability to food-cues in the environment. Indeed, fMRI studies in humans suggest that enhanced activity of amygdale-hypothalamic CPF circuitry in response to food cue presentation is predictive of susceptibility to weight gain [212]. The increase in ORX cell activity during the initial stages of high fat diet consumption is transient in nature, such that following more prolonged periods of exposure to a high-fat diet ORX cell activity normalizes [210], whereas mRNA levels of prepro-orexin gene and OxR2 decrease [213]. By contrast, limited access to a high-fat diet does not influence MCH cell firing. However, prolonged access leads to an increase in mEPSCs frequency likely driven by an increase in excitatory drive onto MCH cells [210]. In addition, elevated MCH and MCH-1R mRNA in LHA results from prolonged access to a high fat diet [214] consistent with a ramping up of MCH system activity. On the other side of the spectrum, chronic administration of ORX and MCH peptide also differentially impact the onset of dietary obesity. Long-term exposure to ORX has no effect on feeding or body weight [215], whereas chronic administration of MCH enhances food intake and obesity in rodents [185, 216]. Taken together, these results indicate that LHA ORX cells may influence weight gain during the early “dynamic” phase, whereas the increase in excitatory drive and activity of LHA MCH cells would set the conditions for further development and maintenance of weight gain during the “static phase” [5], due to the promotion of energy storage through overconsumption, increased sedentary behaviors and reduced metabolism [159, 160, 216, 217].

6.0 Summary

As we navigate our daily lives, each of us frequently experience some degree of hunger. The severity of this drive is dependent on our ongoing energy needs, with the interoceptive feelings generated differing greatly based on the physiological composition of the individual. Nevertheless, mechanisms underlying the generation of hunger uniformly serve to inform the organism that they should engage in behaviors that drive energy intake. From an evolutionary perspective, mechanisms that maintain homoeostatic balance underwent

substantial pressures—after all, if energy needs are not met then the survival of an individual and by consequence the species may be at risk. Accordingly, this suggests conservation across species in the physiological mechanisms underlying body weight control. Interactions between ORX and MCH form a critical physiological allostatic circuit ensuring that these needs for survival can be met. This is achieved in part by flexible and rapid changes in behavioral output that favor relevant and suppress competing appetitive actions.

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Highlights

- The lateral hypothalamic area (LHA) plays a critical role in integrating energetic and reward signaling to regulate food intake
- Orexin/hypocretin (ORX) and Melanin Concentrating Hormone (MCH) cells are localized in the LHA and play a critical role in appetite regulation
- Based on their distribution and functionality, we propose ORX and MCH cells cooperate to respectively mediate flexible transitions from preparatory to consummatory behaviors
- A hypothalamic-striatal circuit underlying control of these behavioral state transitions is described

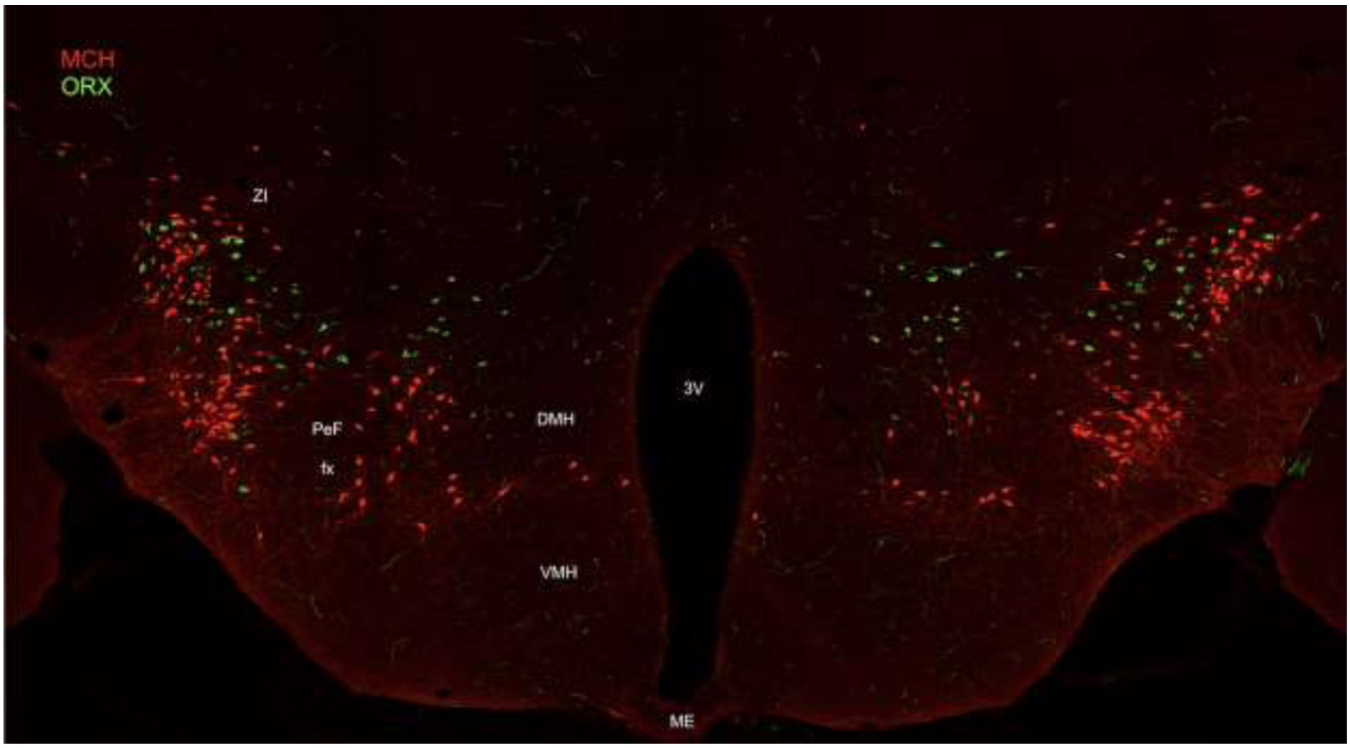

Figure 1: LHA MCH and ORX expressing neurons in the LHA.

Fluorescent labelling of MCH (red) and ORX (green) expressing cells indicates that these neurons form discrete but commingled populations in the LHA. Representative image taken at approximately ~1.7m posterior to bregma from a pMCH-cre mouse crossed with a tdTomato reporter line. Immunohistochemistry was employed to label ORX protein (AlexaFlour 488/ green) and amplify the tdTomato signal (AlexaFluor 568/ red). DMH = dorsomedial hypothalamus; fx = fornix; PeF = perifornical area; VMH = ventromedial hypothalamus; ZI = zona incerta.

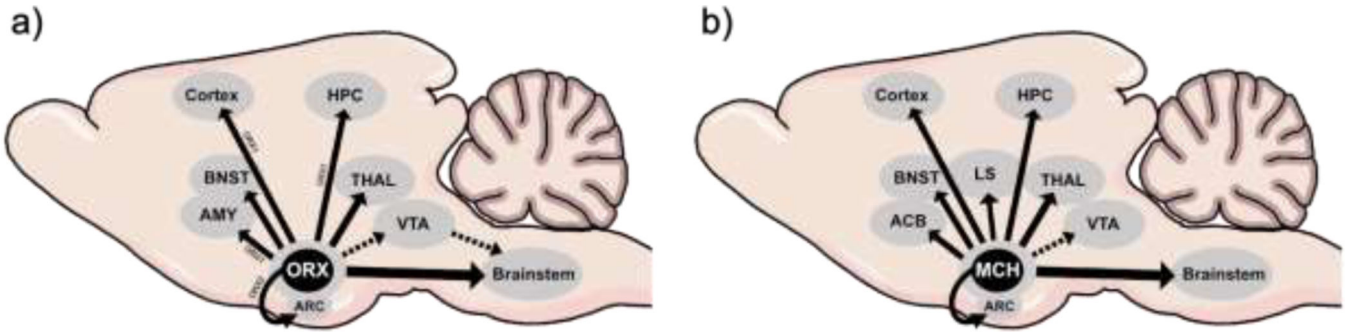

Figure 2: LHA ORX and MCH neuronal projections.

(a) ORX cells project within hypothalamic regions including the arcuate nucleus of the hypothalamus. LHA ORX cells innervate hindbrain regions both through direct connections (solid arrows) to the brainstem as well as indirect ventral tegmental area innervation (dashed arrow). These cells also project to forebrain and limbic regions such as the cortex, amygdala, hippocampus, and thalamus. ORX1 and ORX2 specific projection patterns to specific brain regions are denoted with associated labels. (b) MCH cells project within hypothalamic regions including the arcuate nucleus of the hypothalamus. LHA MCH cells project to the brainstem, cortex, bed nucleus of stria terminalis, lateral septum, nucleus accumbens, and limbic structures such as the thalamus and hippocampus (solid arrows) and debated projection to VTA (dashed arrow). Abbreviations: ACB = nucleus accumbens; AMY= amygdala; ARC = arcuate nucleus of the hypothalamus; BNST = bed nucleus of stria terminalis; HIPP = hippocampus; LS= lateral septum; MCH = melanin concentrating hormone; ORX = orexin; ORX1 = orexin1 receptor; ORX2= orexin 2 receptor; THAL = thalamus VTA = ventral tegmental area.

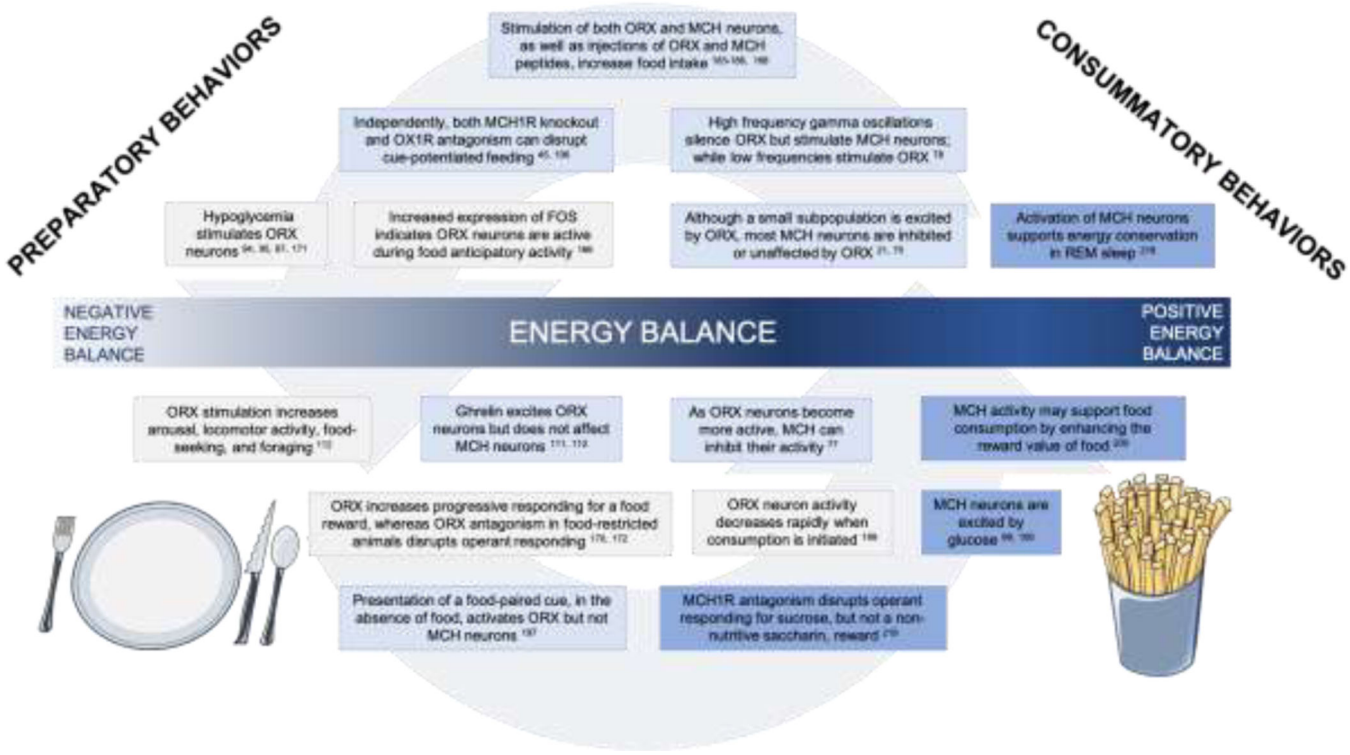

Figure 3. ORX to MCH transitions mediating the appetitive behavioral sequence from food-seeking to consumption.

ICV infusion of MCH [185, 186] increases feeding, as does stimulation of MCH neurons during consumption. Likewise, infusion [183, 184] or chemogenetic stimulation [188] of ORX increases feeding. Knockout of MCH1-R in mice disrupts overeating in cue-potentiated feeding [196] Similarly, antagonism of the OX1R receptor in rats also disrupts cue-potentiated feeding. High frequency gamma oscillations from the lateral septum have the potential to provide input to both ORX and MCH neurons in the LHA; these high frequency oscillations stimulate MCH neurons while silencing ORX neurons [78]. Low blood glucose stimulates orexin neurons [94, 95, 97, 171]. (5) Orexin neurons display increased activation that coincides with food anticipatory activity [166]. MCH neurons are primarily either unaffected or inhibited by ORX [75], although a small (≈ 30%) subpopulation is excited by ORX [21]. MCH neurons are more active during periods of low activity and their activation supports REM sleep [218]. Stimulation of orexin neurons increases overall arousal, as well as feeding-specific behaviors like foraging and food anticipatory activity [112]. Ghrelin, a hunger signal produced in the gut, excites ORX neurons, but appears to have no effect on MCH neurons [111, 112]. MCH neurons can inhibit orexin neurons and appear to do so especially effectively under increased activation of orexin neurons [77]. MCH may support the continued ingestion of food by enhancing its reward value [200]. ICV infusion of ORX-A increased responding for food reward in a progressive ratio task [172], whereas disruption of ORX signaling through ORX antagonism disrupts operant responding under fasted [170] and free-feeding [172]. Orexin neuron activity peaks in anticipation of food consumption but decreases rapidly once consumption is initiated [199]. MCH neurons are excited by glucose [99, 100]. In the absence of food

availability, presentation of a food-paired cue results in ORX, but not MCH, neuron excitation [197]. MCH1-R antagonism disrupts operant responding for a sucrose, but not saccharin reward [219]. Fry and dinner plate illustrations were modified from Smart Servier Medical Art on May 20th, 2020, available online at https://smart.servier.com/category/general-items/food/

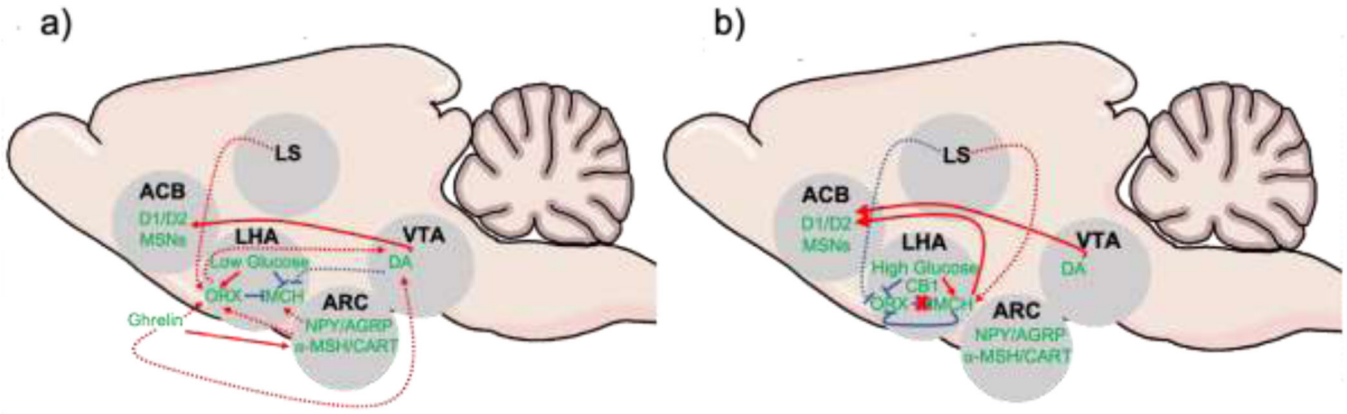

Figure 4. Potential physiological mechanisms underlying ORX to MCH rapid behavioral state transitions for food-seeking and consumption.

(a) Under conditions of hunger, the accompanying low glucose levels stimulates ORX and inhibits MCH. Further, the gastric peptide ghrelin stimulates LHA ORX either indirectly via stimulation of first-order NPY-AGRP neurons in ARC and inhibition of α-MSH and CART signals, or directly via GHSRs in LHA. Increased ghrelin and stimulation of ORX enhances VTA DA, facilitating signaling to ventral striatal ACB MSNs. MCH firing may be inhibited by ORX-dependent increases in GABAergic inhibition and potentially via DA. Finally, lower oscillation frequencies (<10 Hz), ORX cells show a proclivity for stimulation, which could be mediated via LS input. **(b)** As ORX activity increases, MCH can inhibit LHA ORX in an activity-dependent manner. Increased glucose levels following food consumption further attenuate ORX signaling while heightening activity in LHA MCH cells. The CB1 receptor can also respectively inhibit and excite ORX and MCH cells. This general decrease in ORX activity has the potential to disinhibit MCH cell firing. Activity of MCH leads to increases in reward and hedonic pathways in the brain, such as ACB. Abbreviations: ACB = nucleus accumbens; ARC = arcuate nucleus of the hypothalamus; AGRP = agouti-related peptide; α-MSH = α-melanin-stimulating hormone; CART = cocaine and amphetamine related transcript; CB1 = cannabinoid receptor type 1; DA = dopamine; D1/D2 = dopamine D1-like, D2-like receptors; LS = lateral septum; MCH = melanin concentrating hormone; MSNs = medium spiny neurons; NPY = neuropeptide Y. Solid arrows indicate known excitatory (red) and inhibitory (blue) interactions; dashed red arrows = assumed excitatory (red) and inhibitory (blue) interactions that require further pathway characterization.