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Sleep and Metabolism: Implication of Lateral Hypothalamic Neurons

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Abstract

During the last decade, optogenetic-based circuit mapping has become one of the most common approaches to systems neuroscience, and amassing studies have expanded our understanding of brain structures causally involved in the regulation of sleep-wake cycles. Recent imaging technologies enable the functional mapping of cellular activity, from population down to single-cell resolution, across a broad repertoire of behaviors and physiological processes, including sleep-wake states. This chapter summarizes experimental evidence implicating hypocretins/orexins, melanin-concentrating hormone, and inhibitory neurons from the lateral hypothalamus (LH) in forming an intricate network involved in regulating sleep and metabolism, including feeding behaviors. It further confirms the dual sleep-metabolic functions of LH cells, and sheds light on a possible mechanism underlying brain plasticity during sleep and metabolic disorders.

Introduction

Sleep is a primary and essential biological need for higher vertebrates, and sleep-like states have been demonstrated in lower vertebrates [1]. While the functions of sleep are still a matter of debate and may include memory consolidation, brain clearance, and brain plasticity [2], the basic neurobiological mechanisms controlling sleep-wake architecture and sleep functions remain largely unknown. In mammals, there are three vigilance states – i.e., wakefulness, non-rapid eye movement (NREM) sleep (or slow-wave sleep), and rapid

eye movement (REM) sleep (or paradoxical sleep) – characterized by differences in electroencephalogram (EEG), electromyogram (EMG), and electrooculogram (EOG) recordings, fluctuation of brain and body physiological parameters (e.g., temperature, heart rate, breathing) and typical behavioral manifestations. Polysomnography of the waking state is characterized by high-frequency (40–300 Hz), low-amplitude (desynchronized) EEG activity, sustained EMG activity and ocular movements; NREM sleep is characterized by low-frequency (0.5–4 Hz), high-amplitude (synchronized) EEG oscillations, low EMG activity without ocular movement; and REM sleep is defined by predominant theta (6–9 Hz) and gamma (30–300 Hz) EEG rhythms similar to that of waking concomitant to the disappearance of postural muscle tone and the occurrence of REMs and muscle twitches.

The periodic cycling through sleep-wake states relies on a balance between sleep-promoting areas (such as the anterior hypothalamus) and arousal systems, located in the posterior hypothalamus, the basal forebrain, and the brainstem [3–6]. Activity in the latter correlates with wakefulness and states of enhanced arousal, such as alertness or stress, but decreases during sleep (Fig. 1). These arousal systems classically include a distinct neuronal population that produces and releases a complex set of neurotransmitters and neuropeptides/modulators, including norepinephrine, dopamine [7], histamine, acetylcholine, serotonin [8, 9] and hypocretins/orexins (HCRT/OX). Studies have identified a series of neuronal populations throughout the brain that produce and release classical neurotransmitters (GABA, glutamate) implicated in wake control [4–6]. Importantly, optogenetic activation of HCRT/OX neurons induced sleep-to-wake transitions from both NREM and REM sleep [10], through activation of downstream targets, including locus coeruleus neurons from the brainstem [11]. Using opto- or chemo-genetic strategies, the causal involvement of the aforementioned circuits in the control of wakefulness was confirmed, and wake-promoting systems were extended to dopaminergic neurons from the ventral tegmental area (VTA)[7] and the dorsal raphe [12], neurons located in the supramammillary nuclei [13], the external lateral parabrachial nuclei [14, 15], the pedunculopontine tegmental nuclei producing GABA, glutamate or acetylcholine [16], dopamine D1 receptor (D1R)-expressing neurons – co-releasing GABA – in the nucleus accumbens [17], and GABAergic neurons from the superior colliculus [18]. It is important to note that, despite the high degree of redundancy in promoting onset and maintenance of wakefulness, these neural circuits support a variety of arousal-related functions, including attention, anxiety, and stress.

A common feature of these circuits is their widespread ascending projections to the basal forebrain, brainstem, thalamus, neocortex, and hippocampus, where their activity contributes to the high-frequency gamma and low-frequency theta rhythmic activity, typical of wakefulness [19], while their descending projections modulate physiological activity (e.g., somatosensory and motor systems). Hence, these studies collectively emphasize a much more complex mechanism of wakefulness control than previously thought, involving multiple circuits and heterogenous subpopulations of neurons. Interestingly, the same statement is supported by amassing observations of brain circuits implicated in NREM and REM sleep (see below).

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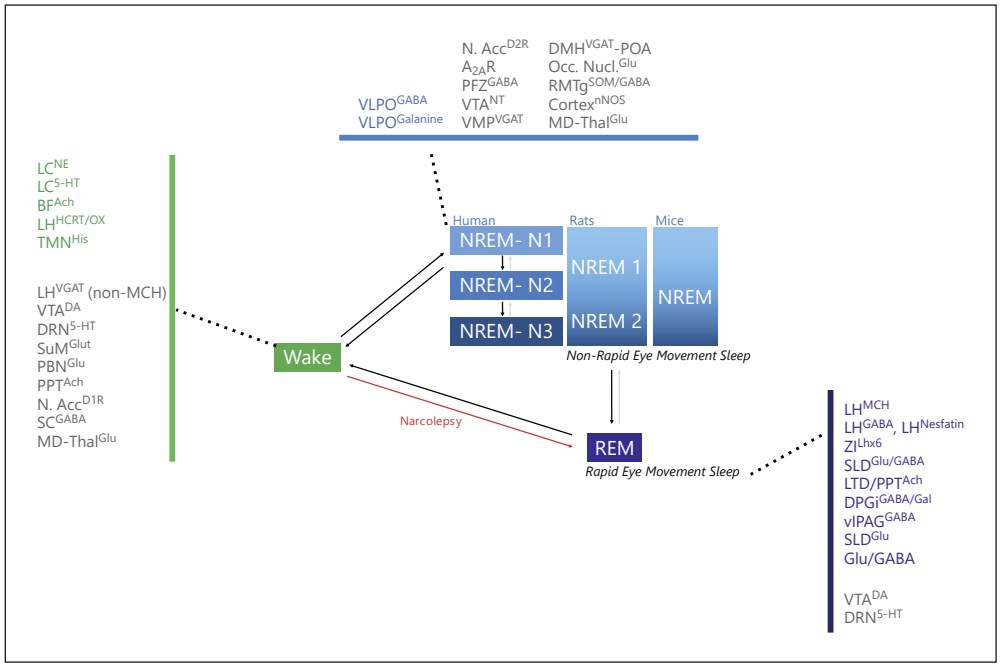

Fig. 1. Cortical and subcortical sleep-wake circuits. Schematic representation of sleep-wake cycle in mammals. Spontaneous (black) and pathological (red, narcolepsy) state transitions are indicated by arrows. Neuronal substrates (associated with specific state of vigilance are listed for wakefulness (green), NREM (light blue), and REM sleep (dark blue). Neuronal populations identified in 2020 using optogenetics are indicated in grey. See main text for functional description of the nuclei. $A_{2A}R$, adenosine A_{2A} receptor; BF, basal forebrain; DA, dopamine; DMH, dorsomedial hypothalamus; DPGi, dorsal paragigantocellular reticular nucleus; DRN, dorsal raphe nucleus; LC, locus coeruleus; LH, lateral hypothalamus; LTD/PPT, laterodorsal/pedunculopontine tegmentum nuclei; MD-Thal, mediodorsal thalamus; N. Acc, nucleus accumbens; Occ. Nucl., occular nuclei; PBN, parabrachial nucleus; PFZ, parafacial zone; PPT, pedunculopontine tegmentum; RMTg, rostromedial tegmental nucleus; SC, superior colliculus; SLD, sub-laterodorsal nucleus; SuM, supramammillary nucleus; TMN, tuberomamillary nucleus; VLPO, ventrolateral preoptic area; VMP, ventromedulla pontine nucleus; VTA, ventrotegmental area; VlPAG, ventrolateral periaqueductal gray; ZI, zona incerta.

At the onset of NREM sleep, the modulatory influence of wake-promoting systems onto subcortical and cortical neuronal populations progressively decreases concomitantly to the increased activity of sleep-promoting systems located in the anterior hypothalamus, basal forebrain, and brainstem (Fig. 1). Original studies using anatomical and functional retrograde and anterograde tract-tracing studies indicated that ventrolateral preoptic nucleus (VLPO) and median preoptic nucleus (MnPo) neurons are synaptically connected with, and fire in, a reciprocal pattern (i.e., opposite) to wake-active neurons. These neurons were later found to comprise multiple subpopulations amongst inhibitory neurons of the anterior hypothalamus that exert a strong inhibitory tone onto wake-active areas of the brain during NREM, as compared to waking [20–24]. Their opto-/chemogenetic activation induced NREM sleep, possibly through an inhibition of wake-active neu-

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rons, including histamine neurons. Interestingly, activation of these subpopulations leads to a variable decrease of body temperature and metabolism, ultimately resulting in a hibernation-like phenomenon [22]. This sleep-temperature response belongs to the physiological changes in the brain and the body that occur at sleep-onset in natural conditions and question the role of hypothalamic neurons as the unique substrate for NREM sleep in the mammalian brain (see below).

In addition, recent causal evidence indicates that extra-hypothalamic neuron populations located in the neocortex [25], neurons from the nucleus accumbens (adenosine A2A receptor, A2AR) [26], GABAergic neurons from the parafacial zone [27], neurotensinergic neurons from the midbrain [28], and GABAergic neurons of the ventral medial midbrain/pons [29], as well as some excitatory neurons from the perioculomotor nuclei [24], zona incerta [30], preoptic area-projecting galanin-expressing GABAergic neurons in the dorsomedial hypothalamus (DMH) [31], somatostatin-positive (SOM+) GABAergic neurons [32], neurons from the midbrain rostromedial tegmental nucleus (RMTg) nuclei [33], as well as striatal A2AR neurons/external globus pallidus parvalbumin neurons involved in adenosine-induced sleep [34], and medio-dorsal thalamic cells [35], were all found to facilitate NREM sleep with variable latencies.

Transitions to REM sleep complete the sleep-wake cycle [36]. REM sleep is characterized by rapid eye movements, muscle atonia, and prominent theta rhythm originating from the hippocampus [37]. Pioneer studies [38] initially located the REM sleep "generator(s)" within the pons, where reciprocal inhibition between neurons in the oralis pontine and sublaterodorsal nuclei (REM-ON) and ventrolateral periaqueductal gray/lateropontine tegmentum (REM-OFF) were hypothesized to gate REM sleep (Fig. 1). More recently, neurons producing the neurotransmitters GABA and glutamate have been integrated into the brainstem circuitry critical for the onset of REM sleep [33]. Importantly, the activity of neurons outside the brainstem also correlates with REM sleep state [19, 39], including neurons located in the anterior and lateral [40–43] parts of the hypothalamus. In particular, neurons expressing the peptide melanin-concentrating hormone (MCH) have been the first to be identified as constituting a REM sleep circuit in the lateral hypothalamus (LH) [43–46].

Additional neurons implicated in brain activity typical of REM sleep, including theta rhythm [47] and eye movement [48], have been identified. For instance, septo-hippocampal structures were demonstrated to mediate theta oscillations that promote sleep-dependent contextual memory consolidation [47]. Neurons in the medio-dorsal thalamus [35] and cortical structures including the claustrum and the retrosplenial cortex [49] were found to be specifically active during REM sleep. Yet, whether these cells are implicated in the onset, maintenance, or termination of REM sleep, rather than its neurophysiological function, remains unclear.

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Beyond Sleep-Wake Circuits

Beside these wake-, NREM- and REM-controlling circuits, a considerable number of neurons exhibit various changes of activity, including subthreshold fluctuation of resting membrane potentials, high firing activity, or transient quiescence during sleep. In this context, whether cells, or neural circuits, are implicated in sleep architecture or sleep function(s), or both, remains to be determined.

In the hypothalamus, inhibitory neurons expressing the vesicular GABA and glycine transporter (LH^{VGAT}) show the highest activity during wakefulness and REM sleep [42], suggesting a contribution of (REM) sleep-dependent neuronal activity to hypothalamic functions during wake. Here, we summarize recent work investigating the role of $LH^{HCRT/OX}$, LH^{MCH} and LH^{VGAT} neurons in sleep and wakefulness, as well as in goal-directed behaviors, including food intake. Based on our latest findings, we will propose a possible role of the dual activity of LH inhibitory neurons during feeding behaviors and REM sleep and discuss how REM sleep may consolidate the encoding of goal-oriented behaviors in the hypothalamus.

$LH^{HCRT/OX}$, LH^{MCH}, and LH^{VGAT} Neurons in Sleep and Metabolism

The LH is a phylogenetically conserved structure in the vertebrate brain that is critical for energy homeostasis, stress response, and goal-oriented behaviors [50]. It plays a key role in integrating hormonal, metabolic, circadian, and motivational signals into coherent behaviors to adapt to an ever-changing environment [51]. These adaptive behaviors also include sleep-wake states.

Anatomical and functional evidence indicates that the LH contains a large diversity of cell populations with complex neurochemical profiles (i.e., transmitters, neuropeptides, and multiple transmembrane receptors) [52] and electrophysiological fingerprints [53, 54]. Those include vesicular glutamate transporter (VGLUT), VGAT, glutamic acid decarboxylase (GAD), neuropeptide Y (NPY), pro-opiomelanocortins (POMC), substance P, dynorphin, nesfatin-1, cocaine and amphetamine-regulated transcripts (CART), histamine, HCRT/OX, MCH, and dopamine (the A11 cell group). These neuronal populations form an intricate local network of excitatory and inhibitory cells, each of which has a specific role in hypothalamic physiological functions. In addition, these populations send widespread projections, often throughout the entire brain, to modulate adaptive behavioral responses.

Electrophysiological recordings of non-overlapping HCRT and MCH neurons, or VGAT and VGLUT neurons, showed that each of these subgroups exhibit typical state-dependent activity across the sleep-wake cycle [41, 42, 55, 56]. Single-cell electrophysiological recordings of unspecified neurons in the LH concluded that most of the neurons were either mostly active during wakefulness, during REM sleep, or during both, but quiescent during NREM sleep [55, 56]. In the following section, we will summarize the circuit

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properties and physiological functions of the main LH cell types, discussing their activity profiles during the different sleep-wake states.

HCRT/OX Neurons

The firing rate of orexin-expressing neurons is highest during active waking or hunger and lowest during NREM and REM sleep and sated states [57–59]. Consistent with this finding, HCRT/OX peptides strongly promote arousal stability and reward [60], and induce feeding [60], although González et al. [61] showed that HCRT/OX ablation also induced feeding. This was originally evidenced by the discovery of the absence of HCRT/OX gene transcripts in the brain of human subjects with narcolepsy/cataplexy, and further established a role for HCRT/OX system (i.e., peptides, cell, and both receptors) in "boundary state control" – i.e., the inability to consolidate periods of wakefulness or sleep [6]. Whether, and how, the lack of HCRT/OX system results in cataplexy, sleep fragmentation, and other symptoms of narcolepsy – hypnagogic hallucinations, sleep-onset REM episodes (SOREMs) – awaits further experimental investigations.

MCH Neurons

The firing rate of MCH-expressing neurons is highest during REM sleep, and lowest during wakefulness and NREM sleep [41]. Accordingly, the MCH peptide was first identified as a feeding-promoting peptide that also dampens energy expenditure [62]. Optogenetic activation of MCH neurons reverses the natural preference for sucrose over sucralose [63], suggesting that MCH neurons participate in sensing the nutritional value of sugar. The sleep-inducing properties of the MCH peptide, in particular REM sleep, was evidenced by pharmacological infusion of the peptide in several brain areas and the expression of the immediate-early gene c-*fos* – i.e., marker of neuronal activity – during the rebound of REM sleep in MCH neurons [40]. Opto-/pharmaco-genetic activation of MCH neurons increased NREM-to-REM sleep transitions and stabilized REM sleep [43, 45, 46], whereas ablation of MCH neurons by cell-specific expression of diphtheria toxin A increased wakefulness and decreased NREM sleep duration [44]. Non-state-dependent activation (i.e., random activation) of these cells also increased the amount of NREM sleep [41, 43, 46]. Recently, MCH neurons have also been associated with the expression of REM sleep when ambient temperature rises [64].

VGAT/VGLUT2 Neurons

LH neurons co-express neurotransmitters together with neuropeptides. As such, larger populations of excitatory (e.g., the VGLUT type 2-expressing LH neurons, LH^{VGLUT2}) and inhibitory (e.g., LH^{VGAT} or $LH^{GAD1,2}$) neuronal population encompass neurons expressing HCRT/OX and MCH peptides, respectively, although some MCH neurons express VGLUT2 [65, 66]. In combination with peptide-specific neuron subpopulations, the study of these larger populations may provide important information on LH physiology.

The firing rate of inhibitory VGAT-expressing (LH^{VGAT}) neurons is high during wakefulness, in particular during initiation of actions leading to retrieval and consumption of

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rewards, and REM sleep, while activity is lowest during NREM sleep [42, 67]. In 2016, we showed that LH^{VGAT} neurons show a transient increase in firing rate during transitions from NREM sleep to wakefulness, suggestive of a wake-promoting role [68]. Accordingly, optogenetic stimulation of LH^{VGAT}, or their projection in the reticular thalamus nucleus, induced a rapid transition to wakefulness during NREM, but not REM, sleep [68]. Consistent with this finding, chemogenetic activation of LH^{VGAT} cells, using the excitatory DREADDs (designer receptors exclusively activated by a designer drug) promoted wakefulness, whereas chemogenetic inhibition, or their optogenetic silencing, prolonged sleep duration [67], possibly through their inhibition of sleep-promoting neurons located in VLPO [67].

Interestingly, during an operant feeding task, LH^{VGAT} neurons clustered either into those regulating appetitive ("food approach") or into those regulating consummatory ("food intake") aspects of feeding behavior [69]. High LH^{VGAT} activity was also observed during reinforcement learning [70, 71] and learning cue-reward associations [72]. This is in line with the increase in food consumption and conditioned place-preference induced by their optogenetic activation, or the opposite responses observed upon optogenetic silencing [69, 72, 73]. This role was further confirmed in an open-field task where gamma phase-locked activity, a computational method suggesting information transfer, between the lateral septum and LH^{VGAT} cells was found to promote the food zone entry but not food consumption [74]. This is consistent with the finding that optogenetic stimulations at frequencies ~ 5 Hz strongly drives food consumption, while higher frequency stimulation preferentially facilitates motivational behaviors, including optical self-stimulation [73].

The firing rate of excitatory VGLUT2-expressing (LH^{VGLUT2}) neurons, some of which may include HCRT/OX neurons [65], across sleep-wake states has not been extensively studied but may have opposite functions to LH^{VGAT} neurons [42]. Activity of LH^{VGLUT2} neurons has been associated with aversive [75] and escape behaviors [76] or with the consumption of a liquid sucrose reward in a satiety-dependent manner [77]. Optogenetic activation of LH^{VGLUT2} neurons in food-deprived subjects induced place aversion and decreased food intake, whereas their inhibition had the opposite effect, possibly through dense projections to the lateral habenula [78], or VTA [72]. These behavioral responses directly depended on the metabolic status of the animal [75].

Collectively, these studies provide a global perspective on how distinct $LH^{HCRT/OX}$, LH^{MCH}, LH^{VGLUT2}, and LH^{VGAT} cell types coordinate apparently antagonistic functions [79]. Yet, the reason for the dual activation of some of these circuits during both wake and REM sleep remains unclear because they are thought to belong to the executive circuits controlling the sleep-wake states, and in particular REM sleep, rather than the function(s) of sleep. However, causal approaches have not yet completely confirmed this hypothesis. In the next section, we will summarize our experimental data suggesting that the activity of LH^{VGAT} neurons during REM sleep, for instance, is essential for the proper maintenance of feeding behavior.

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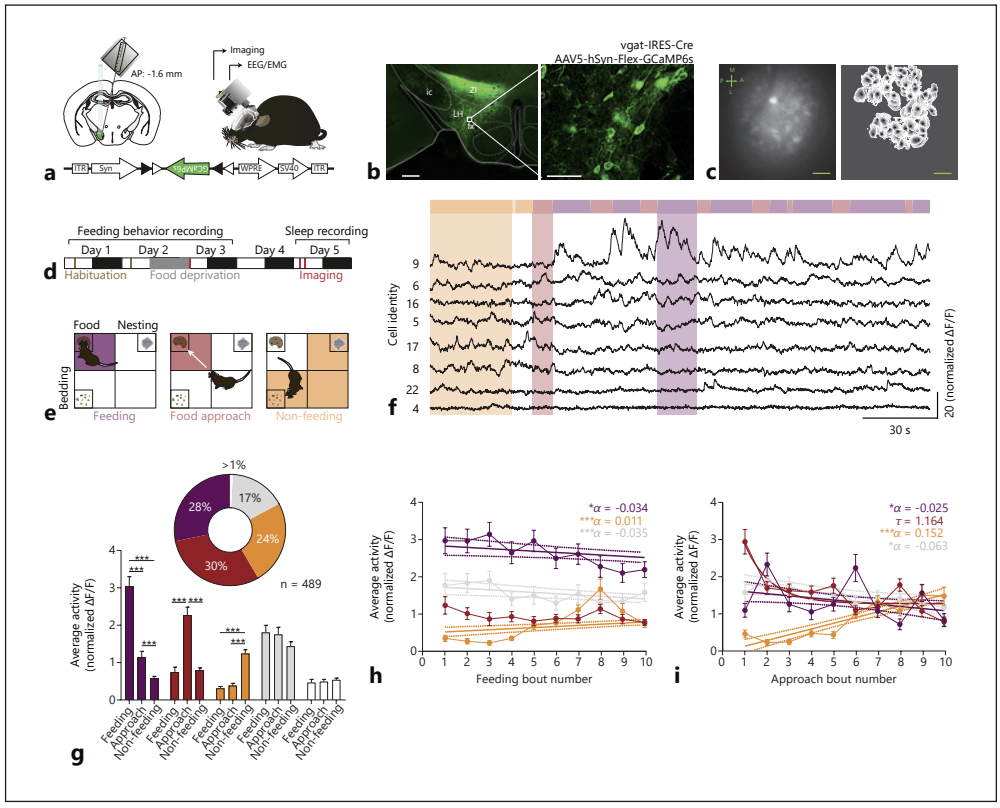

Fig. 2. Feeding is reliably encoded by LH^{VGAT} neurons. **a** Schematic (left) showing LH injection of Cre-dependent AAV in vgat-IRES-Cre mice. Following cre-dependent local virus transfection, the GCaMP6s cassette is flipped in LH^{VGAT} allowing transcription and long-term expression in the LH (bottom). Illustration of the chronic GRIN lens implantation and imaging using a miniature fluorescence microscope in freely moving mice (right). **b** Photomicrograph of cell-specific expression of GCaMP6s in the LH from vgat-IRES-Cre mice 4 weeks after virus injection (left). Right panel shows enlargement of the white box highlighted in left panel. LH, lateral hypothalamus; ZI, zona incerta; fx, fornix; ic, internal capsule. Scale bars: 500 (left) and 50 µm (right). **c** Representative field of view from imaging of LH^{VGAT} neurons with the miniature microscope (left). Bright cellular structures and dark blood vessels are readily visible. Arrows indicate the body axes (A-P, anterior-posterior, M-L, medial-lateral). Cells were identified using the CNMF-E algorithm (right). The single cell activity was longitudinally recorded across multiple experimental sessions. Scale bar: 100 µm. **d** Experimental timeline. White and dark boxes represent light and dark phase, respectively. **e** An open-field arena was divided into four quadrants which contained either food, bedding or nesting material or were left empty. Animals were video-tracked and feeding (purple, left), food approach (red, middle) and non-feeding (orange, right) behaviors were visually scored. **f** Representative recording of calcium transients from GCaMP6-expressing LH^{VGAT} cell across feeding behavior (color-coded, top) acquired at 10 frames per second. 8 single-cell recordings are shown (black, bottom). **g** Mean ± SEM cell activity (normalized ΔF/F) of GCaMP6s-expressing LH^{VGAT} neurons within the different clusters. The pie chart summarizes the classification (n = 489 cells from 5 animals, top). Two-way repeated measures ANOVA followed by Tukey's post hoc test, *** $p < 0.001$. **h**, **i** Mean ± SEM cell activity (normalized ΔF/F) of LH^{VGAT} neurons over consecutive feeding (**h**) or food approach (**i**) bouts by functional cluster (n = 489 cells from 5 animals). Straight lines indicate significant linear regressions ± 95% confidence interval with slope α for different clusters. Note that the activity of food approach-max neurons in (**i**) shows a rapid exponential decay with half-life τ. * $p < 0.05$, *** $p < 0.001$. Reproduced with permission under the Creative Commons Attribution License 4.0 (CC BY) (https://creativecommons.org/licenses/by/4.0/) from Oesch et al. [82].

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LH^{VGAT}, Sleep-Wake States, and Food Intake

The hypothalamus likely plays a role in the "sleep-metabolism" association because it contains neuronal circuits implicated in sleep-wake control and goal-oriented behaviors [79–81]. As described above, LH^{VGAT} cells are active during awake goal-directed behavior and REM sleep. Whether these cells belong to similar, or distinct, clusters and, whether the same neurons are actually active during feeding, wakefulness and REM sleep was unclear, raising the central question as to whether LH^{VGAT} cells contribute to "sleep architecture" or "sleep functions," or both.

In a 2020 study, we took advantage of longitudinal imaging of calcium transients in single LH^{VGAT} cells using microendoscopic technologies in freely-moving mice as a model to understand the contribution of REM sleep to hypothalamic control of food intake [82]. At the single-cell level, we identified functional clusters amongst LH^{VGAT} neurons with maximal activity during "food approach," "feeding" or "non-feeding" behaviors, consistent with previous reports [69]. We showed that these clusters progressively changed over successive feeding bouts; while the activity of "feeding" LH^{VGAT} neurons progressively decreased across consecutive feeding bouts, the activity of "non-feeding" LH^{VGAT} neurons increased, suggesting a rapid adaptation of LH^{VGAT} neurons during ongoing motivational or homeostatic drives (Fig. 2) [82]. At the same time, the representation of feeding behavior at the population level remained remarkably stable. Next, we recorded the activity of the same cells across the different sleep-wake states. Consistent with a previous study [42], we observed that the activity of LH^{VGAT} neurons was strongly modulated across sleep-wake states. Longitudinal imaging revealed two predominant functional clusters of "wake" and "REM" active cells amongst LH^{VGAT} neurons (Fig. 3) [82].

Comparing the classification of LH^{VGAT} neurons during feeding behaviors and REM sleep revealed a large overlap between the feeding-maximally (feeding-max) activated and REM-active neurons, showing that more than 40% of the feeding neurons were reactivated during REM sleep (Fig. 4a) [82]. The intimate link between feeding-max neurons and REM sleep was further confirmed by our finding that their activity was significantly higher during REM sleep than during NREM sleep or wakefulness.

Applying optogenetic silencing of LH^{VGAT} neurons selectively during REM sleep significantly reduced food intake during a subsequent wakefulness period, whereas similar silencing experiments during wakefulness had no effect on feeding behavior (Fig. 4b–g). This decreased feeding was associated with a reorganization of the activity of the LH^{VGAT} neuron population during feeding and food approach that likely reflects a partial remapping of the previously existing clusters.

Collectively, these results suggest that REM sleep stabilizes the hypothalamic representation of feeding behavior and modulates future food intake. This may represent a cellular mechanism to anticipate future metabolic challenges by optimizing cellular representation of behaviors during sleep.

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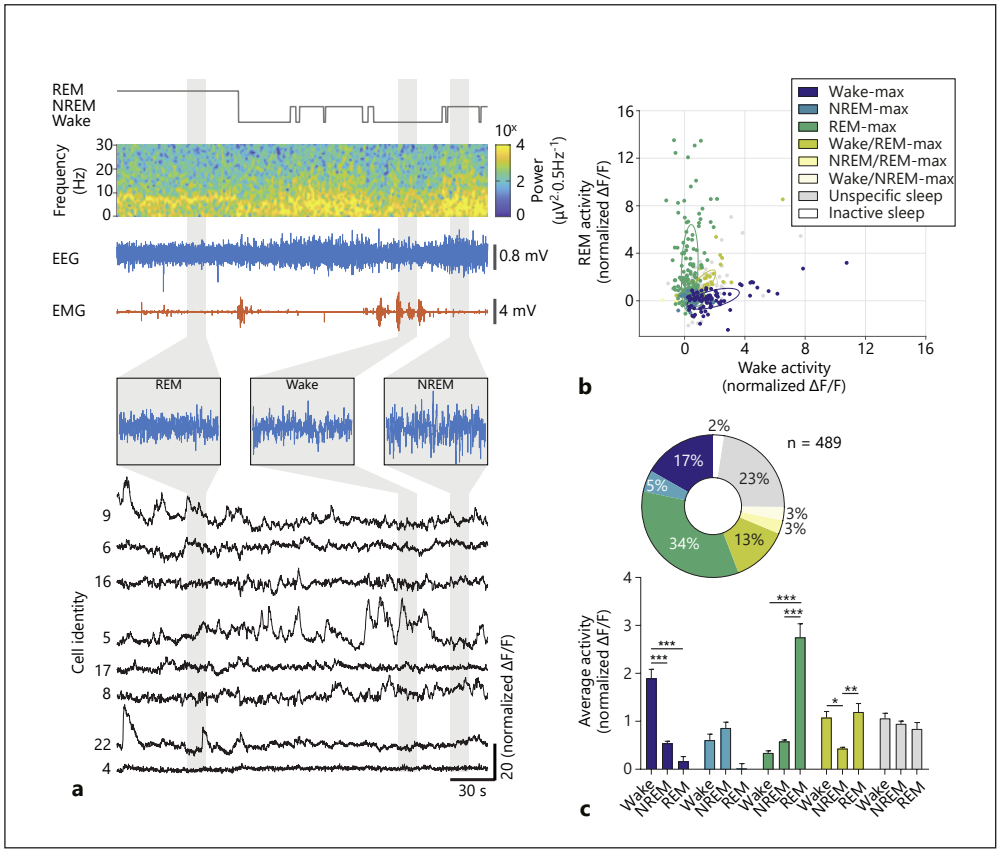

Fig. 3. LH^{VGAT} neurons show high activity during wakefulness and REM sleep. **a** Representative recording of electroencephalogram (EEG), electromyogram (EMG), and calcium transients from GCaMP6s-expressing LH^{VGAT} neurons across sleep-wake states in freely behaving mice. Hypnogram (grey), EEG power spectrum (colormap), EEG (blue), and EMG (red) traces are shown. Insets show extended EEG traces for the different sleep-wake states. Calcium transients for neurons identical to Figure 2f are displayed (black). **b** Scatter plot showing the average activity (normalized ΔF/F) of each LH^{VGAT} cell during wakefulness and REM sleep. Neurons were classified according to their activity profiles during different sleep states. Color-coding indicates cluster identity. Ellipses represent the mean-centered covariance of the clusters for wakefulness and REM sleep. Note that the graph was projected to the two axes of largest variance. **c** Mean + SEM cell activity (normalized ΔF/F) of GCaMP6-expressing LH^{VGAT} neurons within the different clusters encoding sleep and wake states (bottom). The pie chart summarizes the classification of LH^{VGAT} neurons ($n = 489$ cells from 5 animals, top). Two-way repeated measure ANOVA followed by Tukey's post hoc test, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Reproduced with permission under the Creative Commons Attribution License 4.0 (CC BY) (https://creativecommons.org/licenses/by/4.0/) from Oesch et al. [82].

Perspectives

Here, we reviewed some important implications of LH$^{HCRT/OX}$, LH^{MCH}, LH^{VGLUT2}, and LH^{VGAT} neurons in sleep-wake control and goal-oriented behaviors, with an emphasis on their modulation of food intake. LH$^{HCRT/OX}$ and LH^{MCH} neurons have opposite functions

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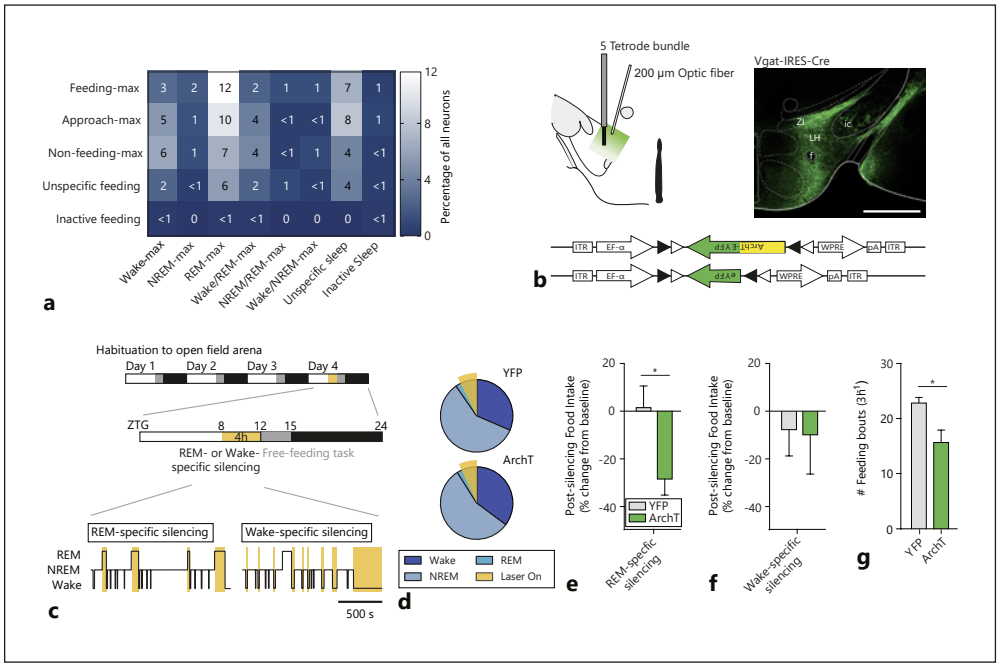

Fig. 4. Optogenetic silencing of LH^{VGAT} neurons during REM sleep, but not wakefulness, decreases food intake. **a** Co-classification matrix of LH^{VGAT} neurons during sleep-wake states and food-directed behaviors. Color-coding and numbers represent the percentage of neurons for the corresponding clusters (n = 489 cell from 5 animals). **b** Schematic of optogenetic targeting and tetrode recordings from freely moving mice (left). Photomicrograph showing cell-specific expression of ArchT in the LH of vgat-IRES-Cre mice (right). LH^{VGAT} neurons were transfected to either express ArchT-EYFP (test group) or EYFP only (control group, bottom). LH, lateral hypothalamus; ZI, zona incerta; f, fornix; ic, internal capsule. Scale bar: 500 µm. **c** Timeline of optogenetic silencing experiment (top). Mice were habituated to the open-field arena for 3 days prior to testing. Online optogenetic silencing (middle) was conducted between zeitgeber (ZTG) 8 and 12, and food-directed behaviors were quantified in a free-feeding task over the next 3 h (ZTG 12–15). Continuous optical stimulation (orange shading) was delivered selectively during REM sleep (bottom left) or wake (bottom right) episodes to silence LH^{VGAT} neurons in a state-specific manner. **d** Average percentage of vigilance states during the REM-specific optogenetic silencing experiment for YFP control (n = 8 animals, top) and ArchT (n = 8 animals, bottom) mice. The orange shading indicates total optogenetic stimulation time during REM sleep. Two-way ANOVA, $p > 0.05$. **e** Average post-silencing food intake change + SEM after REM sleep-specific silencing in YFP control (grey, n = 8 animals) and ArchT (green, n = 8 animals) mice. Student's unpaired t test, * $p < 0.05$. **f** Average post-silencing food intake change + SEM after wake-specific silencing in YFP control (grey, n = 5 animals) and ArchT (green, n = 7 animals) mice. Student's unpaired t test, $p > 0.05$. **g** Average feeding frequency + SEM over the free-feeding task following optogenetic silencing during REM sleep in YFP control (grey, n = 6 animals) and ArchT (green, n = 5 animals) mice. Student's unpaired t test, * $p < 0.05$.

on sleep-wake states and metabolic rate; however, their role on food intake remains controversial depending on the species, techniques and behavioral paradigm used. Yet, LH^{VGLUT2} and LH^{VGAT} encode food intake and possibly aversion, though the latter remains to be confirmed. Thus, it appears that the dissection of their contribution to sleep-wake or

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metabolism is limited by their dual roles in more than one physiological function controlled by the LH that may have direct implications in both sleep and metabolic diseases.

Together, with previous reports implicating LH^{VGAT} neurons in arousal [68], our study suggests that local activity in hypothalamic circuits during REM sleep may not necessarily contribute to the architecture of the sleep-wake cycle, but rather to the optimization of information encoding during that state [82]. Thus, one can speculate that while the activity of "*sleep architecture*" neurons correlates with particular sleep states, its manipulation (with opto-/pharmacogenetics) alters the architecture of the sleep-wake cycle (onset, maintenance, or termination) with various efficacy (latencies, transient effect, etc.), depending on experimental procedures. On the other hand, "*sleep function*" neurons are predominantly active during a given sleep state but may show a non-negligible activity during other states. Importantly, changes in the activity of these neurons do not necessarily alter sleep architecture (e.g., onset, maintenance, or termination of a particular state, NREM-REM cycling, etc.) but rather brain function associated with this sleep-dependent activity.

Interestingly, optogenetic perturbation of this REM sleep reactivation of LH^{VGAT} cells led to a long-lasting decrease in food intake associated with a reorganization of the LH neuronal network supporting food intake. In some ways, this is reminiscent of the reactivation of cortical or hippocampal neuronal assemblies during NREM and REM sleep and the stabilization of internal representation of spatial environment [83–85], reward learning [86, 87], and contextual novelty [47, 88]. Indeed, disruption of these reactivation patterns by electrical or optogenetic closed-loop stimulation selectively, during sharp-wave ripples in NREM sleep, impairs memory consolidation of recently acquired behavior [88, 89]. Furthermore, the neurobiological mechanisms underlying memory consolidation during REM sleep are less well understood and may include place cell replay [84] or theta phase- and amplitude-dependent processes [47, 83]. However, this REM sleep reactivation of inhibitory LH neurons may differ from the classical hippocampus-dependent memory consolidation that is thought to incorporate novel, but not familiar, experience into mnemonic traces during NREM sleep [88, 89]. Indeed, our findings suggest that daily adaptations during feeding behaviors may be updated during REM sleep to optimize the intrinsic representation of feeding behavior and a constant optimization of the behavioral command. Accordingly, we speculate that a daily update would represent an ideal mechanism to revert day-to-day adaptative changes of LH^{VGAT} neuron activity patterns similar to what have been observed during REM sleep modulation of hippocampal neurons [90] or prefrontal network excitability [91].

Collectively, this chapter emphasizes an implication of LH neurons in more than one biological function, as was suggested by the modulation of food intake, wakefulness, arousal, and stress for $LH^{HCRT/OX}$ neurons in the mammalian brain. As shown here for the LH^{VGAT} neurons, such dual implications may lead to an unsuspected role. Therefore, a systematic probing of the role of $LH^{HCRT/OX}$ and LH^{MCH} in multiple physiological tasks is warranted to unravel their integrative functions and their cross talk with other local LH cells types, such as excitatory and inhibitory LH neurons.

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Key Take-Home Points

- $LH^{HCRT/OX}$ and LH^{MCH} have opposite functions on sleep-wake control and metabolism.
- Other local excitatory and inhibitory neurons are active during both food intake and REM sleep.
- REM reactivation of food-active LH inhibitory neurons is essential to maintain food intake.

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Conflict of Interest Statement

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Author Contributions

Both authors were involved in the development and review of the chapter, approved the final version to be published and take responsibility for all aspects of the work.

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