Frontiers in Neuroendocrinology 44 (2017) 27–34

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

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

Review article

# Sleep & metabolism: The multitasking ability of lateral hypothalamic inhibitory circuitries

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ARTICLE INFO

*Article history:*
Received 20 June 2016
Received in revised form 18 November 2016
Accepted 19 November 2016
Available online 21 November 2016

*Keywords:*
Sleep
Metabolism
Food intake
Melanin concentrating hormone
GABA
Hypocretin
Orexin
Histamine

ABSTRACT

The anatomical and functional mapping of lateral hypothalamic circuits has been limited by the numerous cell types and complex, yet unclear, connectivity. Recent advances in functional dissection of input-output neurons in the lateral hypothalamus have identified subset of inhibitory cells as crucial modulators of both sleep-wake states and metabolism. Here, we summarize these recent studies and discuss the multi-tasking functions of hypothalamic circuitries in integrating sleep and metabolism in the mammalian brain.



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## 1. Introduction

Sleep and wakefulness are two mutually exclusive behaviors. Sleep is "*a rapidly reversible state of (behavioral) immobility and greatly reduced sensory responsiveness to environmental stimuli*" (Siegel, 2008). Sleep-like states occur in lower vertebrates and throughout the animal kingdom, suggesting an ancient and strongly conserved mechanism necessary for primary and essential biological needs (but see (Siegel, 2008)). Sleep is important for brain maturation, cognitive processing and metabolite clearance in the brain. Sleep strongly depends on previous activity during wakefulness and prepares the brain and the body for future

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http://dx.doi.org/10.1016/j.yfrne.2016.11.002
0091-3022/

actions, yet our understanding of the neurobiological mechanisms underlying brain control of sleep-wake states is limited.

Here, we briefly summarize neuronal circuits underlying sleep-wake states with an emphasis on hypothalamic circuits. Other excellent reviews have recently summarized brain substrates of sleep-wake cycle (Brown et al., 2012; Fort et al., 2009) and food intake or metabolism (Sternson, 2013; Waterson and Horvath, 2015).

The control of sleep-wake state alternation is supported by distinct cellular networks (neuronal and non-neuronal cells) distributed across the central nervous system. The "stability" of this cycle is important for the proper functioning and the survival of the organism/species. In mammals, states of wakefulness, non-rapid eye movement (non-REM, or slow wave sleep) and rapid eye movement (REM, sometimes called paradoxical sleep) sleep are characterized by distinct electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) signal features and cycle with both ultradian and circadian periods (Brown et al., 2012; Saper et al., 2010). Wakefulness is characterized by high-frequency/low-amplitude cortical EEG oscillations (4–300 Hz), muscle activity and ocular movements.

After prolonged period of wakefulness, sleep pressure – which reflects a process called sleep homeostasis – increases and leads to the onset of NREM sleep. Cortical oscillations show both global and local oscillations composed of slow waves (<1 Hz), high-amplitude delta oscillations (0.5–4 Hz), and spindles (9–15 Hz) accompanied by low muscle activity and the absence of ocular movement. REM sleep is a singular sleep state signalled by predominant EEG theta (6–9 Hz), and a complete disappearance of postural muscle tone (only muscle twitches persist), and fluctuation of the heart and breathing rates accompanied by rapid eye movements are frequently observed during that state. While each of these states is mutually exclusive, sign of intertwined states occur under homeostatic challenge (e.g., sleep pressure or after learning) in local part of the cortex (Funk et al., 2016; Huber et al., 2004; Vyazovskiy et al., 2011).

Although the neurobiological mechanisms controlling the recurrence of these states across a 24 h-period remain unclear, lesion, pharmacological and (opto)genetic studies strongly suggest that the onset, maintenance and termination of wake, NREM and REM sleep states rely on excitation/inhibition between distinct circuits distributed across the entire central nervous system (Fort et al., 2009; Luppi et al., 2016). In particular, unit recording in head-restrained animals revealed that wakefulness is associated with increased activity of the hypocretin/orexin (Hcrt/ox)-expressing neurons in the lateral hypothalamus, the noradrenergic locus coeruleus (LC)-expressing neurons in the brainstem, the serotoninergic dorsal raphe nuclei (DRN) in the brainstem, the histaminergic tuberomammilary nucleus (TMN) in the posterior hypothalamus, the cholinergic pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei in the midbrain, as well as cholinergic neurons in the basal forebrain (reviewed in Brown et al., 2012). During NREM sleep, the activity of thalamo-cortico-thalamic circuits is highly synchronized and generates slow EEG oscillations as shown from *in vivo* recording of freely-moving animals. Similarly, inhibitory neurons in anterior hypothalamic (Alam et al., 1995; Zhang et al., 2015) and brainstem (Anaclet et al., 2014) structures are strongly active, however, their functional link to thalamo-cortical and cortical networks remains unclear. During REM sleep, inhibitory cells from the anterior (Lu et al., 2002) and the lateral (Clement et al., 2012; Jego et al., 2013; Verret et al., 2003) hypothalamus, as well as glutamatergic and GABAergic neurons from the brainstem (Luppi et al., 2006) were found to be strongly active using immediate early gene detection and *in vivo* recordings.

Amassing literature highlighted a dual role for sleep-wake circuits in the brain. For instance, norepinephrine neurons from the locus coeruleus represent a major hub for wakefulness, but also control stress response and attention during cognitive processing (Aston-Jones and Bloom, 1981; Bouret and Sara, 2005). Similarly, sleep and sedation circuits located in the anterior hypothalamus (VLPO, LPOA, etc.) concomitantly regulate body temperature (Schmidt, 2014; Szymusiak and Satinoff, 1981; Zhang et al., 2015). More caudally, neurons in the lateral hypothalamus (LH) expressing hcrt/ox, MCH, GABA and glutamate possess both sensing and controlling modalities, as their firing activity is strongly modulated by metabolic products both *in vitro* and *in vivo* (amino acids, glucose, etc.) (Burdakov et al., 2005; Karnani et al., 2011). Furthermore, the same cell types are also involved in the hypothalamic control of wakefulness, including Hcrt neurons and a subset of LH cells expressing VGAT, and both NREM and REM sleep, as exemplified by MCH cells (see below). These findings are discussed below and support the hypothesis that lateral hypothalamic circuits control both sleep and metabolism through multi-tasking networks. In a translational aspect, clinical and experimental studies report a high prevalence of metabolic syndrome associated with sleep disorders and vice versa. Patients with chronic sleep restriction, fragmented sleep or short sleep night present an increased risk for metabolic pathologies including diabetes and obesity, cardio-vascular risks, mood disorders and hormonal imbalances (Brown et al., 2015; Van Cauter et al., 2008).

This association suggests the existence of underlying circuitries that regulating both sleep/wake states and metabolism, as previously proposed (Adamantidis and de Lecea, 2008). *How sleep-wake circuit shares food intake or metabolic functions?* Both cellular/molecular and recent circuit evidence support these integrative properties amongst hypothalamic circuits. Here, we summarize recent findings linking sleep-wake state and metabolism and discuss lateral hypothalamic mechanisms underlying this patho-physiological associated symptom and point some future direction for the investigation for circuit multi-tasking properties.

## 2. Lateral hypothalamic (LH) circuitries in sleep-wake control

The LH is a homeostasis center that orchestrate food intake, metabolism balance, behaviors directed towards natural- (food, sex) and artificial- (drug) rewards (Bernardis and Bellinger, 1993; Saper et al., 2005; Stuber and Wise, 2016), and sleep-wake states (Brown et al., 2012; Saper et al., 2010). It contains multiple cell types with unique neurochemical profiles, vesicular transporter (s) (Collin et al., 2003; Rosin et al., 2003; Ziegler et al., 2002), connectivity (Ekstrand et al., 2014), membrane receptors (Leinninger et al., 2009) or functions. In contrast to the laminar structure of cortical or hippocampus networks, LH circuitries form an intricate local and extensive network of excitatory and inhibitory cells with no apparent anatomical features. Here, we will summarize recent studies on LH substrates of arousal, sleep and metabolism.

Electrophysiological recordings of LH cells across the sleep-wake cycle identified a wide variety of neurons activity of which correlates with NREM or REM sleep and/or wake states (Brown et al., 2012), suggesting the existence of neuronal (sub)populations with sleep- and wake-inducing properties. Indeed, neurons expressing Hypocretins/Orexins $LH_{Hcrt}$ – ($Hcrt_{1,2}$, also known as $Orexins_{A,B}$ (Sakurai et al., 1998)) and histamine ($LH_{His}$) represent wake-promoting systems (Lee et al., 2005): their cellular activity is typically low during quiet waking and highest during attention and active waking, and ceases firing almost completely during NREM and REM sleep. Accordingly, the activation of the Hcrt system correlates with arousal/alertness associated with a stress response, stress-induced cocaine reinstatement, opioid addiction