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Hypocretins in the Control of Sleep and Wakefulness

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Abstract During the past 10 years since the discovery of hypocretins (Hcrt, also called orexins), the list of their physiologic implications has been growing, from their primary roles in the sleep–wake cycle and feeding to the control of the cardiovascular system, pain, locomotion, stress, and addiction as well as their involvement in psychiatric disorders such as panic, anxiety, and depression. This diverse set of functions is consistent with the localization of Hcrt neurons in the lateral hypothalamus, a major integrating center of sensory inputs and emotional processes, and their widespread excitatory projections throughout the brain. Newly developed optical tools allow us to manipulate the activity of genetically identified neurons with millisecond precision in vivo and to test specific hypotheses about the causal relationships between Hcrt cells and specific behaviors. Here, we review the basic roles of the Hcrt peptides and discuss how these new technologies increase our understanding of the underpinnings of alertness and arousal.

Keywords Orexin · Hypothalamus · Arousal · Optogenetics · Feeding · Narcolepsy

Introduction

In 1998, we identified the hypocretins (Hcrt) as two neuroexcitatory peptides produced in the hypothalamus [1]. In parallel, Sakurai et al. [2] deorphanized two orphan G protein-coupled receptors and identified their ligand as the Hcrt, which they named *orexins*. Twelve years later, this discovery has proved a key element in our understanding of brain mechanisms responsible for the generalized arousal of the central nervous system and the activation of goal-oriented behavioral responses [3]. In this review, we outline how recent studies using new optogenetic methods have refined the role of the Hcrt system in wakefulness and discuss the Hcrt pattern of activity as a key component of adapted behavioral responses.

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Hcrt: A Primary Role in Wakefulness?

The Hcrt (Hcrt-1 and Hcrt-2, also known as orexin-A and orexin-B) are two neuropeptides exclusively produced by a cluster of wake-active neurons in the posterior lateral hypothalamus (LH) [1, 2]. Hcrt neurons have widespread excitatory projections throughout the brain with particularly dense innervations in regions related to wakefulness [4, 5]. Hcrt actions on postsynaptic neurons are mediated by two G protein-coupled receptors, Hcrt receptors 1 and 2 (Hcrt-R1 and Hcrt-R2, respectively [2]), in which major signaling involves G_q protein coupling that results in the activation of phospholipase C and calcium intracellular mobilization. Hence, Hcrt have been shown to increase the firing in most of their targeted structures [6].

Loss of Hcrt neurons and dysfunction in Hcrt neurotransmission are linked to narcolepsy [3], strongly suggesting a prominent role for these peptides in the maintenance of sleep. Pharmacologic and electrophysiologic experiments have converged on the idea that the Hcrt system is a sensor that sets the arousal threshold by integrating various homeostatic signals [7]. The question remained as to

whether endogenous release of Hcrt is sufficient to induce wakefulness. Recently, our laboratory established a causal role between Hcrt neuron activity and sleep-to-wakefulness transitions [8••, 9]. Repeated stimulation of Hcrt neurons increases the number of wakefulness transitions, suggesting a modulatory mechanism by which the Hcrt system promotes the initiation of arousal through the noradrenergic system. These findings were obtained using optogenetic methods to stimulate Hcrt neurons in vivo with high temporal resolution [8••]. Such techniques provide key tools in understanding the specific relationship between Hcrt activity and wakefulness and arousal.

In addition to affecting wakefulness, Hcrt neurons are active in a variety of physiologic situations, most of which may be associated with different states of arousal, such as the control of the cardiovascular system, neuroendocrine regulation, locomotor activity, pain, and stress.

Are the Hypocretins Orexigenic?

However, mainly because of the localization of Hcrt in the LH, considered to be the feeding center, their primary role was thought to be more related to food intake and energy homeostasis. Indeed, early pharmacologic studies linked Hcrt to the regulation of appetite. Intracerebroventricular (ICV) administration of either Hcrt-1 or Hcrt-2 increased food intake in rats [2]. These observations led to the proposal of the alternative name for Hcrt—*orexins*—referring to the orexigenic (appetite stimulant) effect. Local administration of Hcrt-1 in the paraventricular nucleus, the dorsomedial nucleus, the LH, or the perifornical area also has shown an increase in feeding behavior [10].

Although this evidence supports the notion that Hcrt has a physiologic role in food intake, a careful revision of these early studies suggests that the observed effect may be attributed to increased arousal. For instance, most studies showing an increase in food intake used supra-physiologic doses that uniformly increase locomotor activity and goal-seeking behavior. Interestingly, one severe deficit of Hcrt neuron–ablated transgenic mice is the absence of the food-anticipatory increase in wakefulness and locomotor activity in food-restricted conditions [11], suggesting that Hcrt neurons integrate metabolic changes to promote an adapted arousal behavior. Hcrt neurons are localized in the appetite control center and exhibit a reciprocal connectivity with the hypothalamic circuitry that regulates metabolism, including orexigenic neurons in the arcuate nucleus that express neuropeptide Y and anorexigenic cells that express pro-opiomelanocortin [12, 13]. Similar to arcuate neurons, Hcrt activity is directly modulated by peripheral components of the metabolic status, including leptin, glucose, and ghrelin [14, 15]. Leptin concentration in the circulation is proportional to fat stores and produces an anorexigenic signal (appetite suppressant) by notably acting on leptin receptors in the hypothalamus. Hcrt neurons express leptin receptors [16], and prepro-Hcrt mRNA expression is reduced in obese (ob/ob) mice, which lack leptin [17]. Thus, the Hcrt system clearly is linked to energy homeostatic circuits by integrating consistent inputs from the arcuate nucleus and peripheral metabolic signals.

Based on the existing literature, most aspects of Hcrt function may be attributed to a role in sleep–wake regulation and modulation of goal-oriented behavior. Hcrt neurons receive numerous inputs from endocrine and autonomic homeostatic circuits, including those of the circadian cycle. Endogenous Hcrt release also is under circadian control; hypothalamic Hcrt-1 concentrations are highest during the wake-active period of the nocturnal phase in rodents [18]. In both rodents and dogs, fasting does not increase cerebrospinal fluid (CSF) Hcrt levels [19, 20]. This lack of change in release during feeding and food deprivation contrasts with other orexigenic peptides and suggests that some of the food-uptake effect might result from arousal rather than direct feeding pressure. Furthermore, chronic ICV administration of Hcrt-1 in rats, during 7 days, does not modify the daily food intake or cause obesity [21]. Blood glucose, total cholesterol, and free fatty acid levels were normal. However, it should be noted that chronic administration of Hcrt-1 induces a differential response in food intake depending on the sleep cycle. During the diurnal "resting" phase, animals remained awake and, very probably as a consequence, showed an increase in food consumption. Thus, the observed transient increase in food intake induced by pharmacologic injections of Hcrt-1 may be interpreted as a secondary effect in the context of metabolic fluctuations and needs, according to the levels of alertness, motivation, and physical activity.

Hcrt peptides also may be considered as signals at the interface with the metabolic signals and motivational and motor systems to increase food consumption. Hcrt neurons could link homeostatic, hedonic pathways and reward systems involved in appetite regulation. The Hcrt system is closely associated with dopamine-related behavior, notably because Hcrt was found to have a role in driving drug-seeking behavior [22]. Hcrt signaling in the ventral tegmental area is involved in the activation of the mesolimbic dopamine system [23] and the reward-driven appetite [24•]. The primary role of Hcrt in initiating and maintaining arousal may be a crucial step in activating motivational and motor pathways associated with appetite stimulation and feeding behavior. Studies testing the direct role of endogenous Hcrt release on food intake and motivation for palatable food now may be conducted using

optogenetics. This technology may establish a causal relationship between millisecond activation of Hcrt neurons and increase in food intake or food-seeking behavior.

Refining Hcrt Influences on Wakefulness: Transitions or Maintenance?

Studies in mice, dogs, and humans provided very solid evidence that lack of function of the Hcrt system results in narcolepsy and raised a question regarding the normal role of these peptides in the sleep–wake cycle. Narcolepsy is characterized by excessive daytime sleepiness, rapid eye movement (REM) sleep attacks, cataplexy, and loss of muscle tone precipitated by strong positive emotions. Two groups of investigators simultaneously found that a lack of Hcrt-R2 receptor may cause symptoms of narcolepsy in animals, characterized by the inability to remain awake for long periods and sudden episodes of muscle atonia, associated with cataplexy, during the wake-active period [25, 26]. The link between a disruption of the Hcrt system and narcolepsy with cataplexy was strengthened by findings in human patients who showed low or undetectable Hcrt levels in CSF and few Hcrt neurons in the LH [27, 28]. Based on loss-of-function studies, it may be concluded that narcolepsy with cataplexy is a boundary-state control disorder caused by a selective degeneration of Hcrt neurons.

Although Hcrt projections innervate the central nervous system widely, their main targets are associated with arousal and regulation of sleep and waking [4]. Among these, the Hcrt system strongly innervates and potently excites the locus ceruleus, dorsal raphe nucleus, laterodorsal tegmentum, ventral tegmental area, tuberomammillary nucleus, and basal forebrain (BF; Fig. 1b). Direct activation by Hcrt has been described in the locus ceruleus noradrenergic cells, dorsal raphe nucleus serotonergic neurons, ventral tegmental area dopaminergic neurons, and histaminergic tuberomammillary, cholinergic brainstem, and BF nuclei [6].

The serotonergic and noradrenergic systems both have descending connections strongly linked to locomotor control, as well as ascending projections to the forebrain regions involved in cortical activation and sensory integration [29, 30]. Histamine neurons are strongly related to forebrain alerting [31], and dopamine cells are involved in both alerting and reward [32, 33]. Cholinergic cells in the brainstem and BF are known to play a central role in the cortical EEG activation that characterizes wakefulness [34]. Therefore, the Hcrt system may coordinate and maintain the activity of the systems that generate generalized brain arousal and behavior.

Hcrt wake-promoting effects have been shown by several pharmacologic ICV injections of Hcrt-1 and/or Hcrt-2, all resulting in an increase in the time spent awake and a decrease in the time spent in slow-wave and REM sleep [35]. Current models of sleep–wake regulations suggest that Hcrt promote and reinforce wakefulness by directly exciting the ascending arousal systems, notably the brainstem and hypothalamic aminergic cells [36]. Hcrt cells drive these neurons and therefore would be expected to exhibit the same sleep cycle discharge pattern shown by these cell groups. Aminergic neurons discharge maximally during active wakefulness, discharge less in quiet waking and even less in slow-wave sleep, and are inactive during REM sleep, the so-called wake-ON/REM-OFF profile [37]. On the other hand, brainstem and BF cholinergic cells are maximally active in waking, discharge less in quiet waking and slow-wave sleep, but discharge more in REM sleep, sometimes at higher rates than during active waking [37]. Finally, dopaminergic cells fire phasically during wakefulness in anticipation of reward [38] and are also connected by Hcrt [39].

In vivo recordings in rats have shown that Hcrt neurons are active mainly during wakefulness (with an average of 3–10 Hz) and especially correlate during motor activity when animals actively explore their environment [40, 41]. Hcrt cells decrease discharge during quiet waking in the absence of movement and virtually cease firing during sleep. However, Hcrt neurons exhibit phasic discharge with sensory stimuli and in association with REM sleep events, and increase firing during the REM sleep–wake transitions [40, 41]. Hcrt cells are positively correlated with muscular activity as well as fast gamma EEG activity during waking. Compared with other arousal systems, Hcrt neurons are similar to the wake-ON and REM-OFF aminergic cells but exhibit the particularity of being reactivated before cortical activity and return of muscle tone in the transitions from REM sleep to wakefulness.

Recently, our laboratory used optogenetics to manipulate Hcrt neurons with a millisecond temporal resolution during the sleep–wake cycle of freely moving mice [8••]. The photostimulation of Hcrt neurons (from 5–30 Hz) using a light-activated cation channel, channelrhodopsin-2, increased the probability and number of transitions from sleep to wakefulness during both slow-wave and REM sleep [8••, 9]. Only the stimulation of Hcrt cells above 5 Hz, not 1 Hz, resulted in a robust decrease in wakefulness latency. We then were able to establish a causal link between electrical activity of Hcrt neurons and sleep-to-wake transitions and provided evidence that Hcrt are sufficient to induce wakefulness.

The question rising from the aforementioned in vivo observations and those from optogenetics is whether Hcrt cells display a specific discharge pattern/frequency to code for specific behaviors.

It has been hypothesized that tonic firing of Hcrt neurons results in activation of monoaminergic, cholinergic, and

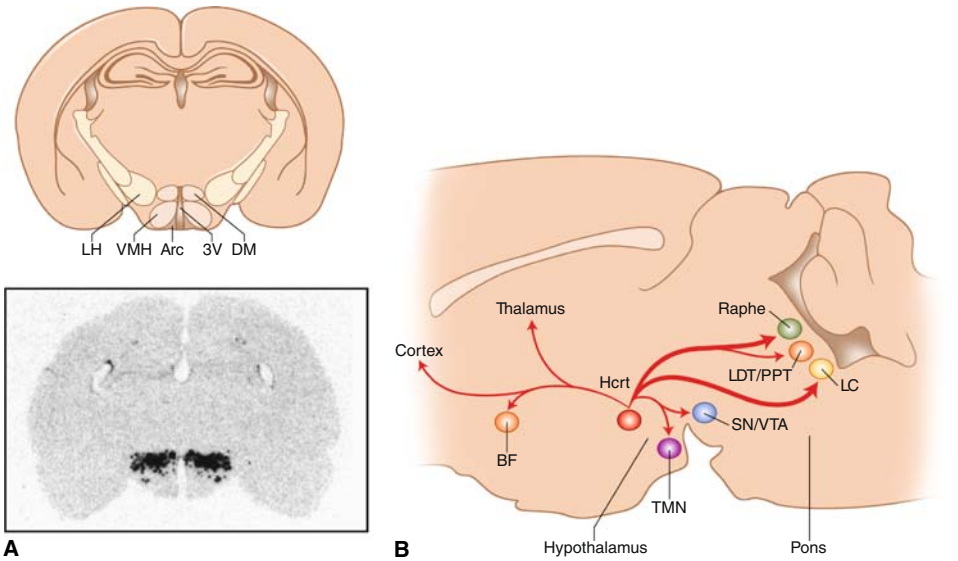

Fig. 1 The hypocretin neuronal system in the rat brain. **a** Schematic drawing of a rat coronal section of the posterior hypothalamic area (*top*) and corresponding photomicrograph (*bottom*) showing the distribution of prepro-hypocretin mRNA-containing neurons (*black grains*) revealed by in situ hybridization histochemistry. **b** Main projections of the hypocretin neurons (*red*) to the wake-activating ascending system including 1) noradrenergic cells (*yellow*) in the locus ceruleus (LC), 2) serotonergic cells (*green*) of the raphe neuronal system, 3) cholinergic neurons (*orange*) in the basal forebrain (BF) and the laterodorsal and pedunculopontine tegmental areas (LDT/PPT), 4) dopamine neurons (*blue*) in the substantia nigra (SN) and ventral tegmental area (VTA), and 5) histaminergic cells (*purple*) in the hypothalamic tuberomammillary nucleus (TMN). 3 V—third ventricle; Arc—arcuate hypothalamic nucleus; DM—dorsomedial hypothalamic nucleus; LH—lateral hypothalamic area; VMH—ventromedial hypothalamic area

amino acid neurotransmitter systems during wakefulness and periods of maintained muscle tone. The release of Hcrt at these times may occur continuously, through the spontaneous discharge of these cells. Tonic activity of Hcrt cells during waking would extend the duration of waking periods and block the onset of sleep, sustained by the correlation between wakefulness and the circadian fluctuations of Hcrt extracellular concentrations [18, 42] or c-fos immunoreactivity through the sleep–wake cycle [43]. During slow-wave and REM sleep, the tonic effects of Hcrt on nonadrenergic and serotonergic cell groups would be blocked by GABAergic inhibition in the LH that may be local or, more likely, may come from the ventral preoptic sleep center [36].

However, there are some indications that a phasic activity of the Hcrt neurons also may be a key signal to attain arousal stability. Hcrt neurons can fire phasically during waking in response to sensory stimuli [40]. Phasic release of Hcrt therefore may be associated with sudden strong emotions, potentially triggering cataplexy in narcoleptic patients and animals. The Hcrt phasic activity at frequencies higher than 5 Hz would lead to peptide release and may counteract inhibiting effects that could be induced by a very strong emotion, contributing to the maintenance of alertness. Trains of Hcrt activity at frequencies between 8 and 20 Hz were observed during 10 s coinciding with transitions between REM sleep and wakefulness [40, 41]. Similarly, the pattern of stimulation of Hcrt cells used by optogenetics, resulting in increased wakefulness transitions, may be associated with an acute phasic discharge.

How then would Hcrt stabilize the vigilant state? The mechanism may involve a bimodal action of Hcrt: 1) phasic activity essential for transition of vigilant states and possibly for generating immediate, higher levels of alertness and 2) tonic, probably extrasynaptic release required to maintain long episodes of wakefulness under circadian control. However, the modality of the Hcrt phasic activity remains to be determined relative to specific behaviors/emotions (goal-oriented behavior, reward, anxiety, stress, or even learning). Loss-of-function studies in knockout mice abolished all Hcrt activity (both phasic and tonic), thus they cannot provide conclusions about the role of either type of activity. In contrast, newly developed optogenetic methods now allow us to directly discriminate between tonic and phasic activity of Hcrt neurons.

Another possible mechanism of wake stabilization may come from synaptic scaling of the Hcrt circuit. Synaptic scaling is a form of plasticity that facilitates transmission in synapses according to the previous history of release. During sleep, Hcrt synapses are mostly inactive; therefore, the probability of their release increases as sleep pressure decreases. When homeostatic conditions permit, this increase in probability triggers the phasic firing of Hcrt neurons, eliciting wakefulness. During wakefulness and increased locomotor activity, Hcrt synapses would be upscaled. This hypothesis is consistent with recent data

showing that cortical activity, possibly driven by Hcrt release, is affected by how long the animal has been awake or asleep [44].

Conclusions: Revising Pathology

The concentration of Hcrt-1 in the CSF in humans has been established as a diagnostic tool for narcolepsy with cataplexy [45]. Anatomic experiments have shown that in this condition, Hcrt mRNA and protein are virtually absent [28]. Other markers of Hcrt neurons, such as dynorphin and NARP (neuronal activity-regulated pentraxin), also are absent in narcoleptic brains, suggesting that these cells have degenerated rather than downregulated Hcrt transmission [46, 47]. In contrast, very few, if any, neurologic diseases have shown consistent alterations in Hcrt signaling. A recent notable exception is the finding that patients with panic disorders display increased levels of Hcrt-1 in their CSF [48•]. This finding is consistent with previous data from our laboratory associating increased Hcrt activity with hyperarousal. In panic disorders, sustained Hcrt release may be so dramatic that significant changes may be detected in a comparatively large volume of CSF. Other pathologies involving hyperarousal, such as chronic stress, posttraumatic stress disorder, and addiction, also may be linked to increased Hcrt transmission. Newly developed orally available Hcrt receptor antagonists may be used as selective therapeutic tools to treat these conditions [49•].

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