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The brain hypocretins and their receptors: mediators of allostatic arousal

Matthew E. Carter, **Jana Schaich Borg**, and **Luis de Lecea**
Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA 94304

Abstract

The hypocretins (abbreviated "Hcrts"—also called "orexins") are two neuropeptides secreted exclusively by a small population of neurons in the lateral hypothalamus. These peptides bind to two receptors located throughout the brain in nuclei associated with diverse cognitive and physiological functions. Initially, the brain Hcrt system was found to have a major role in the regulation of sleep/wake transitions. More recent studies indicate Hcrts may play a role in other physiological functions, including food intake, addiction, and stress. Taken together, these studies suggest a general role for Hcrts in mediating arousal, especially when an organism must respond to unexpected stressors and challenges in the environment.

Introduction

It has been a decade since the discovery of the hypocretins (Hcrts), and during the past ten years we have learned much about their expression, structure, and function. Almost immediately after their discovery, the important role of Hcrts in maintaining wakefulness was reported in multiple species including humans [1–5]. Subsequent years have only solidified the evidence that Hcrts are both necessary to maintain and sufficient to induce wakefulness, and they are now generally considered to be "arousal-promoting" peptides [6–7]. Recently, Hcrts have also been implicated in physiological functions and behaviors other than wakefulness. In this review, we provide an overview of the brain Hcrts and their receptors and survey the recent studies implicating a role for Hcrts in these diverse physiological functions. In trying to integrate these studies, we suggest that two general functions of Hcrts are to mediate wakefulness and allostatic arousal.

The hypocretins

The Hcrts were discovered independently by two groups in the late 1990s [8,9]. They consist of a pair of secreted peptides, hypocretin-1 and hypocretin-2 (Hcrt1 and Hcrt2; also known as "orexin A" and "orexin B", respectively). These peptides are processed from the same genetic precursor, "preprohypocretin" (ppHcrt) and are expressed exclusively in the perifornical lateral hypothalamic area of the brain [8,9]. Hctrs and their receptors are also expressed in the periphery [10], but in this review we focus on Hctrs of the central nervous system.

Brain Hcrt neurons receive afferent projections from many nuclei in the hypothalamus, the allocortex, claustrum, bed nucleus of the stria terminalis, periaqueductal gray, dorsal raphe nucleus, and lateral parabrachial nucleus [11]. Hcrt neurons receive input from GABAergic, glutamatergic, and cholinergic neurons [12]. Furthermore, *in vitro* electrophysiology studies

Corresponding author: Luis de Lecea, Ph.D, 701B Welch Road, Stanford University, Stanford, CA, 94304, Phone: 650-736-4389, Fax: 650-725-4913, llecea@stanford.edu.

demonstrate several neurotransmitters/neuromodulators excite Hcrt neurons (including corticotropin releasing factor, ghrelin, neurotensin, vasopressin, and oxytocin) or inhibit Hcrt neurons (including serotonin, noradrenalin, dopamine, neuropeptide Y, and leptin) [13].

In turn, Hcrt neurons project to diverse areas of the central nervous system, including prominent projections to the noradrenergic locus coeruleus (LC), the histaminergic tuberomammilary nucleus (TMN), the serotoninergic raphe nuclei, the dopaminergic ventral tegmental area (VTA), the cholinergic pedunculopontine tegmental area (PPT) and laterodorsal tegmental area (LDT), and the galaninergic ventrolateral preoptic nucleus (VLPO) [14]. Hcrt neurons also project diffusely throughout the cerebral cortex. Hcrts are excitatory peptides and therefore depolarize their efferent targets [8,9].

Taken together, these anatomical and electrophysiological studies suggest that Hcrt neurons integrate a variety of homeostatic signals from the central nervous system and periphery, and project to numerous brain regions, many which express other neuromodulators and are capable of regulating diverse physiological functions and behaviors (Figure 1).

The hypocretin receptors

Both Hcrt peptides bind with different affinities to two Hcrt receptors, hypocretin receptor 1 (Hcrtr-1—also called “OxR1”) and 2 (Hcrtr-2—also called “OxR2”) [8,9]. Hcrt-r1 binds Hcrt1 with high affinity and binds Hcrt2 with 100 to 1000-fold lower affinity [9,15]. Hcrt-r2 has a high affinity for both Hcrt1 and Hcrt2 (Figure 2).

The Hcrt receptors are located on postsynaptic terminals in a pattern consistent with the anterograde projections of hypocretin neurons described above (Figures 1 and 2) [6,8,9,14]. Hcrt-r1 mRNA is detected within the hypothalamus, the LC, the cerebral cortex, and several brainstem nuclei. In contrast, Hcrt-r2 mRNA is expressed in cholinergic nuclei in the brainstem, the ventral tegmental area, and TMN, as well as overlapping expression with Hcrt-r1 in the hypothalamus. Partially due to a lack of specific antagonists (Box 1), little is known about the distinct functions of Hcrt-r1 and Hcrt-r2. However, Hcrt-r2 knock-out animals, but not Hcrt-r1 mice, show narcolepsy, and therefore supporting a prominent role for this receptor in arousal stability.

Box 1

Pharmacological perturbation of the Hcrt system

Given the important role of the Hcrts in sleep and other neurological disorders, many pharmaceutical companies have attempted developing agents to target the Hcrt system *in vivo* [49]. The most often used Hcrt antagonist in the literature is SB-334867 [50]. This antagonist can be injected systemically and reversibly blocks Hcrtr-1 binding, although it is not clear whether it affects Hcrtr-2 binding as well. SB-334867 has been used in many *in vitro* studies of Hcrt neurons but also in over 100+ *in vivo* studies, elucidating the role of Hcrts in many behaviors including food intake, sleep, stress, and addiction.

The newest Hcrt receptor antagonist, ACT-078573 (“Almorexant”) [51], can be administered orally, readily crosses the blood-brain barrier, and reversibly blocks both Hcrt receptors with high affinity. Perhaps more importantly, in preliminary trials this compound does not elicit cataplexy (despite what might be predicted from an efficient antagonist to both Hcrt receptors), making it an exciting prospect for insomnia treatment. Thus, ACT-078573 will likely be the subject of much future study, both at the lab bench and in the clinic.

There are currently no potent Hcrt agonists that can be used *in vivo* other than the two Hcrt peptides themselves. In animal research, these peptides are often directly microinjected into discrete brain regions or injected intracerebroventricularly into the brain's ventricular system. However, in humans and animals, Hcrt peptides are relatively ineffective when injected systemically [52]. Therefore, narcolepsy or cataplexy symptoms are most often treated using compounds that target other brain arousal systems. For example, Modafinil is approved by the FDA for the treatment of narcolepsy and other sleep disorders. This wake-promoting compound probably inhibits the dopamine transporter, but the exact mechanism of action is unknown [52].

Given the newly discovered roles of the Hcrt system in food-intake, reward processing, stress, vigilance, and depression, it is enticing to speculate that manipulation of the Hcrt system may be useful for the treatment of disorders such as obesity, drug addiction, anxiety, attention-deficit disorder, or depression. At least some of these potential treatment options are now feasible, given the development of the new and improved Hcrt receptor antagonists described above.

The crucial role of hypocretins in arousal stability

Extensive evidence demonstrates that Hcrts promote and maintain wakefulness, as described more thoroughly in other excellent reviews [6–7,13]. Major evidence stems from the original finding that impairment of the Hcrt system causes the sleep disorder narcolepsy in mice, dogs and humans [1–5]. Most human narcoleptics have decreased levels of Hcrt in their cerebrospinal fluid, and postmortem analysis reveals a reduction of Hcrt neurons in human narcoleptic brains [4,5]. Interestingly, the Hcrt system is also necessary for normal emergence from general anesthesia [16]. Intracerebroventricular (i.c.v.) injection of Hcrt1 and/or Hcrt2 increase the time spent awake and decrease the time spent in slow-wave and REM sleep in a variety of vertebrate species [17–18]. Furthermore, artificial stimulation of Hcrt neurons using a light-activated cation channel, channelrhodopsin-2, increases the probability of transitions from sleep to wakefulness during both slow-wave and REM sleep [19]. Thus, there is now solid evidence that Hcrts are necessary to maintain and sufficient to induce wakefulness.

Other potential functions of the hypocretin system

Hcrts are implicated in many physiological functions other than maintaining wakefulness. For example, the alternate name of Hcrts, "orexins", was designated because i.c.v. infusion of Hcrts increased food intake in rodents [9]. These results are now considered to be an indirect effect of the wake-promoting effects of Hcrts, but this is still an active area of investigation. Microinjection of Hcrts into the arcuate nucleus stimulates orexigenic GABAergic neurons and inhibits anorexigenic POMC-expressing neurons. Hcrts also inhibit neurons in the ventromedial hypothalamus, an established satiety center [20]. Thus, Hcrts act in a reciprocal manner to the satiety hormone leptin in important energy-homeostatic regions of the hypothalamus.

Recently, an exciting role for Hcrts has been established in reward-seeking and addiction. Activation of Hcrt neurons is correlated with cues associated with drug and food reward. Stimulation of Hcrt neurons or microinjection of Hcrt1 into the VTA or ventricles reinstates previously extinguished drug-seeking behaviors, and these effects are blocked by a Hcrtr-1 antagonist [21,22]. These seminal studies have sparked a rapidly growing body of research that repeatedly confirms Hcrts modulate reward processing [23].

Stimuli that increase arousal/wakefulness also often increase stress and anxiety. Therefore, the ability of Hcrts to promote wakefulness suggests that these peptides may play a role in increasing the behavioral and physiological hallmarks of stress. In support of this hypothesis, i.c.v. injection of Hcrt1 elicits many stress-related behaviors [17,24]. Increased Hcrt activity is also correlated with a variety of stress-related autonomic processes, such as elevation of mean arterial blood pressure, heart rate, oxygen consumption, and body temperature [25–27]. Moreover, Hcrt fibers project to corticotropin releasing factor (CRF) neurons within the paraventricular nucleus (PVN) [28–29], neurons that activate the hypothalamus-pituitary-adrenal (HPA) axis organismal response to stress. Bath application of Hcrt1 elicits depolarization and increased spike frequencies in these CRF cells [28]. This evidence suggests that Hcrts may interact with central CRF systems to activate the HPA axis and other stress-related processes.

In addition to food intake, addiction, and stress, Hcrts have also been implicated in rodent models of attention [30] and male sexual behavior [31]. Hcrts have also been hypothesized to play a role in the symptoms of Parkinson's Disease [32], schizophrenia [33–34], and depression [35–36]. In sum, studies of the Hcrt system have progressed far beyond the initial discovery of the involvement of Hcrts in sleep and wakefulness. These studies beg the question: How can Hcrts play a role in such a diverse arsenal of behaviors ranging from wakefulness to food intake, addiction, stress, vigilance, and even sexual behavior? Below, we provide a preliminary answer to this question.

Hypocretins: regulators of arousal and allostasis

The role of the hypocretin system in promoting wakefulness is often described as a role in "arousal." Generalized arousal is marked by increased motor activity and heightened responsiveness to sensory and emotionally salient stimuli [37–40]. Less often emphasized, however, is that arousal systems are involved in much more than just regulating sleep/wake cycles, such as the vigilance, anxiety, and symptoms of many psychiatric disorders [41]. Importantly, brain structures implicated in generalized arousal, including the reticular formation of the medulla and pons, midbrain, and the paraventricular, dorsomedial, and lateral hypothalamic nuclei [42], receive projections from Hcrt neurons. We propose that if Hcrts can modulate this arousal network, they are also likely able to modulate behaviors orchestrated by this network. By appreciating the role arousal is known to play in such behaviors studied outside the sleep field, investigators may be able to make increasingly novel yet specific hypotheses about the function of Hcrts in non-sleep behaviors. For example, recent reports that Hcrts modulate behavior in murine models of depression [35–36] is understandable and even anticipatable in the face of years of psychiatric research showing that arousal processing is impaired in humans with depression [43].

Hctrs seem to have their greatest influences when arousal is needed to regulate basic homeostatic pressures like hunger, anxiety, or the drive for sex. Therefore, we propose that Hcrts are particularly important for allostasis. In contrast to homeostasis, allostasis maintains stability at levels outside the normal range and is achieved by varying the internal milieu to match perceived and anticipated environmental demands [44,45]. For example, consider a recent study testing the effects of calorie restriction on stress and depression [46]. Work linking stress and depression shows that preprohypocretin knockout mice and Hcrt neuron-ablated mice show reduced stress responses to acute and chronic stressors [47]. However, some stress responses are preserved, both to acute stress induced by the forced swim test and chronic stress induced by chronic social defeat. This stress causes symptoms of depression [46]. Fascinatingly, under allostatic pressure, Hcrts can actually inhibit stress-induced depressive symptoms, reinstating "homeostatic" control of brain arousal. Calorie-restricted mice perform better in a forced swim test (have longer latencies to immobility and less total

immobility) and do not exhibit social interaction deficits compared to *ad libitum*-fed mice. Hcrt null mice do not show either of these calorie-restriction benefits. Moreover, the number of c-Fos positive Hcrt neurons induced by calorie restriction correlates strongly with improvement on the social interaction test [46]. This suggests that Hcrt neurons mediate an allostatic generalized stress response to calorie restriction that allows an animal to overcome maladaptive depressive symptoms induced by chronic stress. Similarly, although Hcrts do not necessarily stimulate food intake under normal conditions, in situations of calorie-restriction, Hcrts are necessary for adaptive increases in food-anticipatory behavior [48]. This study further demonstrates that Hcrt neurons mediate allostatic changes in behavior, in this case ensuring that animals will be awake and motivated to obtain food during the limited times it is available. While more research is needed to understand the functions of Hcrts in different types of environmental challenges, these examples illustrate how the physiological functions of Hcrts will only be fully uncovered when we appreciate the role of Hctrs in homeostasis and allostasis.

Conclusions

In the ten years since their discovery, we have learned much about the brain Hcrt system. Indeed, the role of Hcrts in promoting wakefulness is indisputable. This review suggests a framework for thinking about a general role for Hcrts in other behaviors as well. While more research is needed to elucidate the precise functions of Hcrts, perhaps the role of the Hcrt system will only be fully appreciated in the context of organismal homeostasis and allostasis. With sophisticated new imaging and optogenetic technologies, the next ten years will no doubt contain continued advances in our understanding of this fascinating brain arousal system.

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Box 2

Unresolved questions about the hypocretin system

- Are there functional subdivisions within Hcrt nuclei? It has been suggested that there are at least two discrete functional populations of Hcrt neurons: a lateral population playing a role in food intake and addiction, and a more medial population playing a role in arousal and stress [53]. Future studies are needed to test this hypothesis.
- Do the two Hcrt receptors differentially regulate distinct physiological functions and behaviors? Are they both necessary for regulating a behavior, or is a single receptor sufficient?
- Do Hcrt neurons promote wakefulness by projecting to many sites in the brain, or just a few key populations of neurons? Several models of sleep/wake circuitry, such as the flip/flop model of sleep, suggest that Hcrt enhances an awake state by projecting to other arousal centers such as the LC, TMN, and dorsal raphe nuclei [7]. However, lesions of these nuclei do not lead to a robust phenotype and normal wakefulness is maintained, even when all these nuclei are ablated in the same animal [54]. Thus, the postsynaptic sites necessary to mediate the action of Hcrt neurotransmission are still unclear.
- What allostatic pressures are necessary or sufficient to drive Hcrt-mediated arousal? How do environmental pressures translate into activation of the Hcrt system?

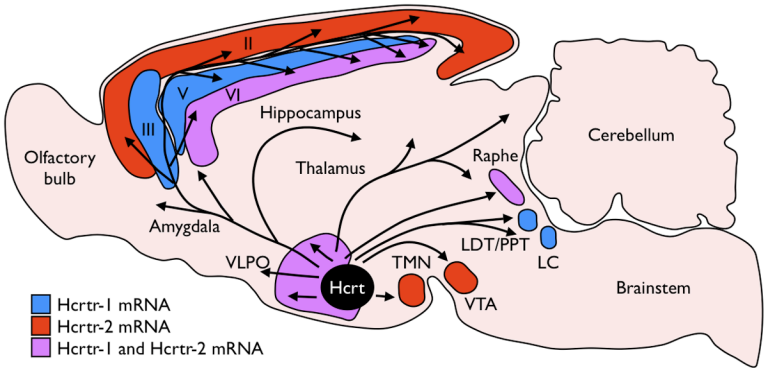

Figure 1. Afferent projections of hypocretin neurons and expression of hypocretin receptors

Hcrt neurons project widely throughout the brain, including the LC, TMN, VTA, dorsal raphe nuclei, other hypothalamic nuclei, and the cortex.

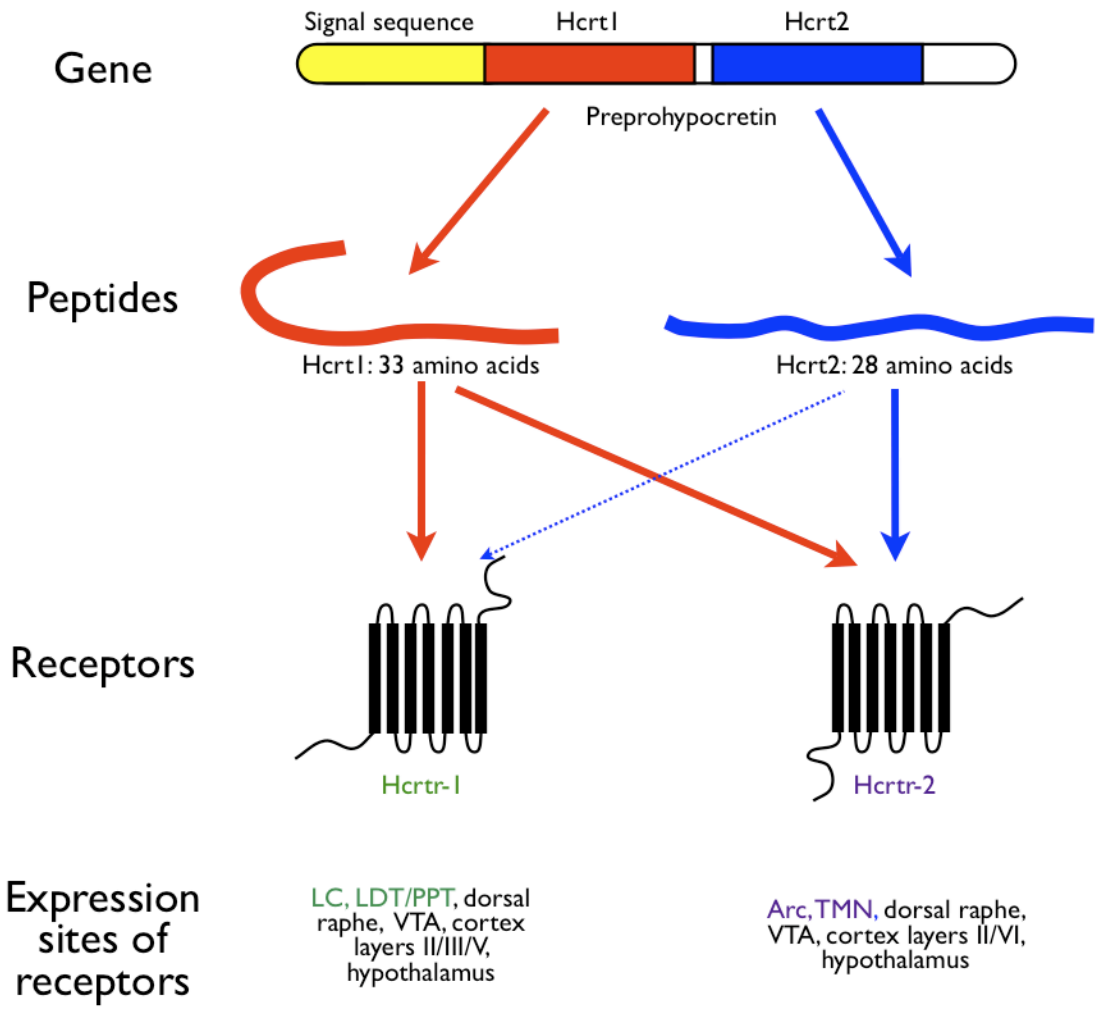

Figure 2. The brain hypocretins and their receptors

Hcrt1 and Hcrt2 are both spliced from the same genetic precursor, Preprohypocretin. Hcrt1 binds with high affinity to both Hcrt receptors, while Hcrt2 only binds with high affinity to Hcrtr-2. Hcrt receptors are differentially expressed throughout the brain, with Hcrtr-1 expressed in the LC and LDT/PPT, and Hcrtr-2 expressed in the TMN. Modified from [14].