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Research Report

The role of hypocretin in driving arousal and goal-oriented behaviors

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ABSTRACT

The hypocretins (Hcrts), also called orexins, are two neuropeptides secreted by a few thousand neurons restricted to the lateral hypothalamus. The Hcrt peptides bind to two receptors located in nuclei associated with diverse cognitive and physiological functions. Experimental evidence has demonstrated that the physiological roles of hypocretins extend far beyond its initial role in food consumption and has emerged as a key system in the fields of sleep disorders and drug addiction. Here, we discuss recent evidence demonstrating a key role of hypocretin in the motivation for reward seeking in general, and drug taking in particular, and we delineate a physiological framework for this peptidergic system in orchestrating the appropriate levels of alertness required for the elaboration and the execution of goal-oriented behaviors. We propose a general role for hypocretins in mediating arousal, especially when an organism must respond to unexpected stressors and environmental challenges, which serve to shape survival behaviors. We also discuss the limit of the current experimental paradigms to address the question of how a system normally involved in the regulation of vigilance states and hyperarousal may promote a pathological state that elicits compulsive craving and relapse to drug seeking.

1. Introduction

It has been a decade since the discovery of the hypocretins (Hcrts), and during these past 10 years we have learned much about their expression, structure, and multiple physiological functions (Sakurai et al., 1998, de Lecea and Sutcliffe, 2005). A few thousand Hcrt neurons, which are restricted to the perifornical area in the lateral hypothalamus, receive afferent projections from many nuclei within the hypothalamus and from the cortex, claustrum, bed nucleus of the stria terminalis, periaqueductal gray, dorsal raphe nucleus, and lateral parabrachial nucleus (Yoshida et al., 2006). Besides, Hcrt neurons receive input from GABAergic, glutamatergic, and cholinergic neurons, and *in vitro* electrophysiology studies demonstrate that several neurotransmitters/neuromodulators excite Hcrt neurons (including corticotropin releasing factor, ghrelin, neurotensin, vasopressin, and oxytocin) or inhibit Hcrt neurons (including serotonin, noradrenaline, dopamine, neuropeptide Y, and leptin). In turn, Hcrt neurons project to the noradrenergic locus caeruleus (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) (for a review, see Carter et al., 2009b) (Fig. 1).

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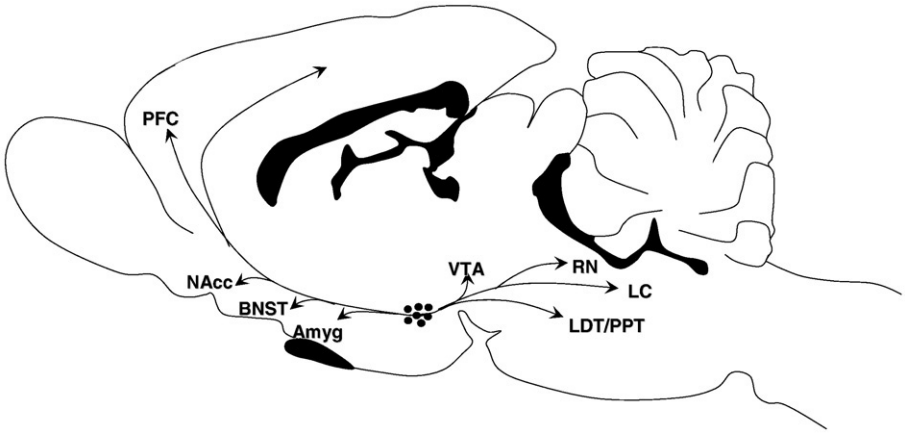

Fig. 1 – Hypocretin producing neurons (dots) are restricted to the lateral hypothalamus and project throughout the brain, in particular to brain regions involved in arousal, stress and brain reward. PFC: prefrontal cortex; NAcc: nucleus accumbens; BNST: bed nucleus of the stria terminalis; Amyg: amygdala; VTA: ventral tegmental area; RN: raphe nucleus; LC: locus caeruleus; LDT/PPT: laterodorsal tegmentum and pedunculopontine tegmentum.

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'). Hcrtr-1 binds Hcrt1 with high affinity and binds Hcrt2 with 100- to 1000-fold lower affinity. Hcrtr-2 has a high affinity for both Hcrt1 and Hcrt2. The Hcrt receptors are located on postsynaptic terminals in a pattern consistent with the anterograde projections of Hcrt neurons described above. Hcrtr-1 mRNA is detected within the hypothalamus, the LC, the cerebral cortex, and several brainstem nuclei. By contrast, Hcrtr-2 mRNA is expressed in cholinergic nuclei in the brainstem, the ventral tegmental area, and TMN as well as overlapping expression with Hcrtr-1 in the hypothalamus (for a review, see Carter et al., 2009b).

Thus, the Hcrts interact with autonomic, neuroendocrine, and neuroregulatory systems, including monoamine neuromodulators and the HPA axis, and project to all the major components of the limbic system as well as brain areas involved in the regulation of arousal, stress, and motivation (for a review, see Sutcliffe and de Lecea, 2002, Sakurai, 2007). Not only Hcrt neurons act as sensors for metabolism and arousal (Adamantidis and de Lecea, 2009) and drive appropriate levels of alertness in function of metabolic needs (Yamanaka et al., 2003), but they also may be involved in triggering sustained attention/arousal associated with the execution of goal-oriented behaviors (Adamantidis and de Lecea, 2008).

2. The hypocretins and the maintenance of behavioral state boundaries

Extensive evidence supports the notion that Hcrt peptides are agents that promote waking (Chemelli et al., 1999; Lin et al., 1999; Hara et al., 2001; Peyron et al., 2000; Thannickal et al., 2001). For instance, intracerebroventricular (i.c.v.) injection of Hcrt1 and/or Hcrt2 increases the time spent awake and decrease the time spent in slow-wave and REM sleep in a variety of vertebrate species (Piper et al., 2000; Espana et al., 2001). Further, two different animal models with an impaired Hcrt system – genetic narcoleptic dogs with a mutation in the Hcrt receptor 2 gene (Lin et al., 1999) and mice with a null mutation of the preprohypocretin gene that produces Hcrt-1 and Hcrt-2 peptides (Chemelli et al., 1999) – showed symptoms of narcolepsy, suggesting that impairment of the Hcrt system may underlie the syndrome of human narcolepsy. Human narcoleptic patients exhibit a dramatic reduction (85–95%) in Hcrt-1 in the cerebrospinal fluid (Nishino et al., 2000) and in the number of Hcrt neurons (Peyron et al., 2000; Thannickal et al., 2001) leading to the hypothesis that narcolepsy could be related to ongoing loss of Hcrt neurons (van den Pol, 2000). In the current models, the Hcrts stabilize the firing of brainstem neurons that promote wakefulness and REM sleep (cholinergic in the LDT/PPT nuclei, noradrenergic in the LC, serotonergic in the dorsal raphe nucleus, and histaminergic in the tuberomammillary nucleus). Interestingly, Hcrts also have a strong and direct excitatory effect on the cholinergic neurons in the basal forebrain that contribute to cortical arousal, but they have no effect on sleep-promoting GABAergic neurons within the ventrolateral preoptic area (Eggermann et al., 2001).

Noteworthy is the facilitatory role played by the Hcrt system for normal emergence from general anesthesia (Kelz et al., 2008). 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 (Adamantidis et al., 2007), although such an artificial stimulation of Hcrt neurons remains ineffective after a 2- to 4-h sleep deprivation (Carter et al., 2009a). Thus, there is now solid evidence that Hcrts are necessary to maintain and sufficient to induce wakefulness.

3. The hypocretins and attentional processes

In addition to the prominent role of the Hcrt system in arousal stability, the extensive innervations of intralaminar thalamic nuclei and prefrontal cortex suggest a role for Hcrt in attention and executive function (Fadel et al., 2002). Interestingly,