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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.

Introduction

It has been a decade since the discovery of the hypocretins (Hcrts), and during these past ten years we have learned much about their expression, structure, and multiple physiological functions (Sakurai 2009, 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,

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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 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) (for review, see Carter et al., 2009b). 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 100–1000-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 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 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).

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 (Pieper 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., 2000) 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-hour sleep deprivation (Carter et al., 2009a). Thus, there is now solid evidence that Hcrts are necessary to maintain and sufficient to induce wakefulness.

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, narcoleptic patients exhibit attention difficulties that can not be attributed to sleepiness only (Rieger et al., 2003).

Anatomical and functional observations have reported a role for Hcrt-1 in depolarizing a limited subset of cortical neurons in the deeper layers (Bayer et al., 2004). Initially, Hcrt was shown to excite thalamocortical terminals predominantly in the prefrontal cortex; nicotine could act synergistically by binding nicotinic receptors in excitatory thalamocortical terminals in other regions of the cortex (Lambe and Aghajanian, 2003a, 2003b). Compelling evidence established a role for Hcrt-2 in attention and it has been proposed that Hcrt-2 and nicotine receptors are part of a common underlying mechanism for enhancing performance under conditions of high attentional demand (Lambe et al., 2005).

High density of Hcrt immunoreactive fibers and receptors suggest the PVT is an important target of Hcrt function in arousal, autonomic functions and limbic activities. Huang and colleagues investigated the effects of Hcrt-2 on neurons projecting from the paraventricular nucleus of the thalamus (PVT) to the medial prefrontal cortex (mPFC), and concluded that the robust excitation of Hcrt-2 on cortically projecting excitatory PVT neurons could serve as a state-amplifier for the action of Hcrt arousal systems to enhance cortical arousal and attention, particularly with regard to limbic and visceral states (Huang et al., 2006).

In line with these observations, Hcrt cells discharge with maximal activity during exploratory behavior, which can be considered as sustained attention or alertness (Mileykovskiy et al., 2005). Systemic or intracerebral administration of the Hcrtr-1 antagonist SB 334867 disrupted attentional performance in rats (Boschen et al., 2009). These observations strongly suggest a role for Hcrt in sustained attention, and possibly in the execution of goal-oriented behaviors. Dominant rats exhibiting risk-taking behavior display augmented acquisition of operant responding for palatable liquid reward that correlated with increased Hcrt receptor mRNA in the mPFC relative to subordinate and control rats (Davis et al., 2009). This observation further suggests a role for Hcrt in goal-oriented behaviors, possibly by orchestrating the appropriate level of alertness for specific goals.

The hypocretins and the pursuit of natural rewards

Reducing Hcrts to endogenous modulators of illicit drug seeking behavior would be a major misunderstanding of the physiological role of this peptidergic system. Hcrt neurons are sensitive to glucose, leptin (Yamanaka et al., 2003), triglycerides (Chang et al., 2004), pH and carbon dioxide concentrations (Williams et al., 2006). Nevertheless, Hcrts do not seem to be critical players in food intake behaviors, but rather adapt arousal and motivation levels to allow feeding and drinking behaviors (Adamantidis and de Lecea, 2008). Depending on physiological needs (hunger, thirst), Hcrts elicit appropriate level of arousal to engage exploratory and goal-oriented behaviors, which can ultimately strengthen motivation for palatable food and liquids (Borgland et al., 2009; Thorpe et al., 2005; Kunii et al., 1999) or lead to the reinstatement of a previously extinguished food seeking behavior in an operant conditioning paradigm (Boutrel et al., 2005; Nair et al., 2008). It seems, however, that the Hcrts do not drive alertness elicited by physiological needs only, but in response to psychological needs as well.

Recent evidence suggests that Hcrt potentiates male sexual behavior in rats (Gulia et al., 2003; Muschamp et al., 2007) in a way that facilitates the energized pursuit of sexual engagement. Strikingly, higher Hcrt-1 content was found in mid brain, medulla and thalamus harvested at late proestrus relative to all other stages of the sex cycle in female rats (Russell et al., 2001). These observations are considered to reflect greatest release of Hcrt-1 into nerve endings in brain areas implicated in sex cycle-specific behaviors, such as lordosis and sexual receptivity in female rats (Russell et al., 2001). More importantly, it is often claimed that if the most reinforcing behavior in male rats is copulation, whereas the main reinforcing behavior in females is maternal care. Not surprisingly, Hcrt-1 modulates maternal behavior in mice (D'Anna and Gammie, 2006). Hence, not only Hcrt drives appropriate levels of alertness in response to thirst and hunger, but it triggers sexual arousal and sustained maternal care. It is then tempting to suggest a role for Hcrt in adapting/strengthening coping strategies in animals facing desire and needs.

The hypocretins and sustained drug seeking behaviors

The identification of the Hcrtergic system as an important component of the brain reward pathways has sparked a great deal of interest in the construct of arousal and hyperarousal (Borgland et al., 2006; Boutrel et al., 2005; Carr and Kalivas, 2006; Georgescu et al., 2003; Harris et al., 2005; Hollander et al., 2008; Lawrence et al., 2006; Narita et al., 2006; Wise 2006). Hcrt is nowadays considered as a major player in the regulation of drug seeking and drug taking behaviors, as much as other peptide systems like CRF, opioids, cannabinoids and nociceptin (for review, see Shalev et al., 2009). The implication of Hcrt in psychostimulants, opiates and alcohol seeking and taking have been extensively discussed elsewhere (Aston-Jones et al., 2009; Boutrel, 2008, Lawrence, 2009).

The first evidence linking the Hcrt system to drug addiction was the report on the diminished signs of precipitated opiate withdrawal displayed by mutant mice deficient in Hcrt (Georgescu et al., 2003), an observation that was confirmed recently in C57BL/6J mice with a Hcrtr-1 antagonist (Sharf et al., 2008). The second and pivotal observation was the

demonstration that c-Fos activation of lateral hypothalamic (LH) Hcrt neurons correlated with preference for an environment repeatedly paired with food and drug rewards. Consistent with this observation, it also was reported that activation of LH Hcrt neurons (or infusion of Hcrt-1 directly into the VTA) reinstated an extinguished preference for an environment repeatedly paired with natural and non natural reward in rats, and that a morphine priming injection activated LH Hcrt neurons of extinguished rats (Harris et al., 2005).

Parallel experiments showed that Hcrt signaling in the VTA was required for behavioral sensitization to cocaine (Borgland et al., 2006). This conclusion was drawn after daily administration of SB334867, a Hcrtr-1 antagonist, either systemically or intra-VTA for 5 consecutive days, 15 min prior to cocaine injections. This pretreatment significantly blocked the development of cocaine sensitization in Sprague-Dawley rats. In line with this observation, it was later reported that sensitization to amphetamine resulted in preferential activation of c-Fos in Hcrt neurons, whereas no activation was reported following acute amphetamine treatment (McPherson et al., 2007). Interestingly, when given only on day 6, SB334867 did not reduce locomotor activity, indicating that while Hcrt receptor signaling is required for the development of cocaine (and most likely amphetamine) sensitization, it is not required for its expression (Borgland et al., 2006).

The impact of the Hcrt system on amphetamine and cocaine intake remains unclear. Infusion of the Hcrt-1 peptide directly in the lateral ventricle did not change cocaine intake in either rats exposed to the drug for one or six hours a day (Boutrel et al., 2005). When rats were trained to self-administer cocaine using a progressive ratio schedule of reinforcement, the final ratio (e.g. number of infusions) obtained by rats before termination of the session remained unchanged after infusion of the peptide or the receptor antagonist (Boutrel et al., 2005, Smith et al., 2009a). This observation suggests that either activation or blocking of the Hcrt receptor system has no consequence on psychostimulant consumption in a self-administration procedure. However, a recent report claims that blockade of Hcrtr-1 (with the Hcrtr-1 antagonist SB 334867) selectively reduces work to self-administer cocaine in rats (Borgland et al., 2009). Hence, the role of the Hcrts in cocaine consumption remains unclear, but the availability of new Hcrt receptor ligands may bring new insight on this subject.

Importantly, whatever the role of Hcrts on cocaine taking might be, it has been clearly shown that i.c.v. infusions of Hcrt-1 lead to a dose-related reinstatement of a previously extinguished cocaine seeking behavior in rats (Boutrel et al., 2005), an observation later confirmed with local infusions of the peptide directly into the VTA (Wang et al., 2009). Further, pretreatment with the Hcrtr-1 antagonist SB 334867 was shown to prevent footshock-induced reinstatement of a previously extinguished cocaine seeking behavior (Boutrel et al., 2005).

Recent reports have demonstrated the ability of the Hcrtr-1 antagonist SB334867 to decrease both alcohol and nicotine self-administration behaviors (Corrigall, 2009; Hollander et al., 2008; Lawrence et al., 2006; Richards et al., 2008), while administration of Hcrt directly into the PVN or in the LH increases ethanol-drinking in rats without affecting food and

water intake (Schneider et al., 2007). Importantly, blocking of the Hcrt system also prevents cue-induced reinstatement of previously extinguished alcohol-drinking behavior (Lawrence et al., 2006). The impact of the Hcrt system on opiate intake has not been reported yet, but the observations demonstrating a role for the Hcrt system in mediating the expression of precipitated morphine withdrawal (Georgescu et al., 2003; Sharf et al., 2008), as well as the absence of preference for a compartment previously paired with morphine administration in Hcrt-deficient mice (Narita et al., 2006) rather suggest a real potential for Hcrt in the regulation of opiates seeking and taking behaviors.

In sum, daily pretreatment with the Hcrtr-1 antagonist SB334867 prevents cocaine sensitization but does not block daily cocaine intake in a self-administration procedure (Borgland et al., 2006; Smith et al., 2009a). In contrast, a single injection of the Hcrtr-1 antagonist prevents both Hcrt-, footshock-and cue-induced reinstatement of a previously extinguished cocaine seeking behavior (Wang et al., 2009; Boutrel et al., 2005; Smith et al., 2009), but does not reduce the acquired cocaine-induced increased locomotor activity (Borgland et al., 2006). Besides, whereas blockade of Hcrtr-1 does not reduce psychostimulant consumption (Smith et al., 2009a), blocking Hcrt receptor signaling reduces both nicotine and alcohol intake in rats (Hollander et al., 2008; Lawrence et al., 2006). Hcrtr-1 blockade appears as a promising drug target to prevent relapse for alcohol and morphine seeking (Lawrence et al., 2006; Harris et al., 2005), as well as for nicotine seeking.

The hypocretins between brain reward and brain stress systems

Concordant observations point to a role for Hcrt-1 in driving cocaine seeking through activation of the mesolimbic dopamine system. In particular, Hcrt-1 has been shown to be critically involved in cocaine sensitization through the recruitment of NMDA receptors in the VTA (Borgland et al., 2006). Reinstatement of cocaine seeking has been reported after stimulation of Hcrt cells within the LH (Harris et al., 2005) or after direct infusion of the peptide into the VTA (Wang et al., 2009). Infusion of the Hcrtr-1 antagonist SB334867 directly into the VTA prevents morphine-induced place preference (Narita et al., 2006).

The anatomical and functional interactions between corticotrophin releasing factor (CRF), a major component of the acute stress response, and Hcrt are well documented. CRF terminals make synaptic contacts with Hcrt perikarya and depolarize genetically identified Hcrt neurons through CRFR1 (Winsky-Sommerer et al., 2004; for review, see Berridge et al., 2009). Reciprocally, Hcrt neurons activate the HPA axis, probably via stimulation of CRF neurons in the paraventricular hypothalamus (Samson et al, 2007). However, intra-VTA infusion of a corticopin releasing factor (CRF) receptor antagonist does not prevent Hcrt-induced reinstatement of lever pressing behavior, and intra-VTA infusion a Hcrtr-1 antagonist does not affect footshock-induced reinstatement of an extinguished lever pressing activity previously paired with cocaine consumption (Wang et al., 2009). These results suggest that CRF and Hcrt act independently on the mesolimbic dopamine mechanisms of cocaine seeking (Wang et al., 2009).

Hcrt-1 may reinstate cocaine seeking through induction of a priming effect (e.g., a cocaine-like rewarding effect). However, the elevated intracranial self-stimulation (ICSS) thresholds observed after Hcrt-1 infusion into the lateral ventricle rather suggests a decrease in excitability of brain reward systems (Boutrel et al., 2005). Indeed, such an elevation of ICSS thresholds is in sharp contrast to the cocaine-induced lowering of ICSS thresholds that is considered to reflect an increased sensitivity that underlies, or at least contributes to the positive affective state associated with drug consumption. In contrast, this long-lasting reward deficit is similar to that observed after i.c.v infusion of CRF (Macey et al., 2000) or after drug withdrawal (Markou et al., 1991; Epping-Jordan et al., 1998). Hence, this observation provides strong evidence suggesting that Hcrt-1 reinstates cocaine seeking by mechanisms different from increased dopamine release. Further, compelling evidence has established that the Hcrtr-1 antagonist SB-334867 decreased nicotine self-administration and also abolished the stimulatory effects of nicotine on brain reward systems, as measured by reversal of nicotine-induced lowering of ICSS thresholds (Hollander et al., 2008). It is important to note that same doses of SB-334867 administered alone did not modulate ICSS thresholds, suggesting a limited impact of tonic Hcrt transmission on the regulation of baseline sensitivity of brain reward systems.

In sum, a non-physiological activation of the Hcrt system using peptide infusion (either in the lateral ventricle or in the VTA) powerfully reinstates reward seeking. We claim that the prevention of Hcrt-induced reinstatement of cocaine seeking by the blockade of CRF and noradrenergic systems (Boutrel et al., 2005), important components of brain stress pathways known to play a role in stress-induced reinstatement (Shalev et al., 2009), suggests that Hcrt and stress systems may closely interact to regulate reward seeking behaviors, and that these interactions occur in brain areas different from the VTA. Meanwhile, Hcrt transmission may contribute to drug-induced activation of brain reward circuitries and thus may contribute to shape a novel equilibrium in brain circuitries that may lead to novel priorities regarding reward seeking in an intoxicated organism.

However, further studies are needed to address these questions. Main observations published over the past few years have been mainly based on pharmacological tools. And despite their important contributions, most of these studies report the effect of SB334867 (Rodgers et al., 2001), a Hcrtr-1 antagonist that may cross interact with Hcrtr-2 and other neurotransmitters. To date, very limited observations have been reported with Hcrt-deficient mice. And these mutant mice also raise the problem of brain systems forced to adapt and counterbalance innate deficiencies. New perspectives come from new ways of probing lateral hypothalamic Hcrt network with unprecedented cellular and temporal resolution (Adamantidis et al., 2007; Zhang et al., 2007). It is tempting to suggest that the optogenetic control of Hcrt neurons may reveal how drug addiction may hijack the normal regulation of goal-oriented behaviors and precipitates compulsive drug seeking after a history of drug intoxication.

The hypocretins and the probing of local lateral hypothalamic circuits regulating motivation for reward seeking

Hcrt-containing neurons account for only 10–30% of all neurons in the LH region, and are surrounded by multiple neuronal subtypes with excitatory, inhibitory and complex

modulatory properties (e.g. NPY/AgRP, POMC/CART, Hcrt, MCH). Therefore, correlations between cellular activity and specific behavior using classical methods of manipulation of brain function, including pharmacological tools, lesions and electrical stimulations may be difficult to interpret. Some of these limitations have been partially overcome by the use of mouse genetics including gene knockouts, mutations and targeted neuronal ablations. To circumvent the lack of specificity and low temporal resolution of these approaches, newly developed methods to manipulate membrane potential of predefined cell populations provide unprecedented opportunities to dissect neuronal network activities (Zhang et al. 2006; Sjulson & Miesenbock, 2008). For instance, optogenetics uses light-sensitive cations channels (channelrhodopsin-2) or ionic pumps (halorhodopsin or NpHR (Natronomonas pharaonis halorhodopsin); for review, see Zhang et al. 2007) to selectively depolarize or hyperpolarize specific neuronal cell groups with millisecond time scale temporal resolution. Genetic targeting of ChR2 or NpHR into defined classes of hypothalamic neurons allows bimodal manipulation of specific circuit activity and avoids the inadvertent stimulation of neighboring neurons that occurs with electrical stimulation. Thus, optogenetics may be use to deconstruct the connectivity and manipulate the plasticity of intermingled hypothalamic circuits (e.g. Hcrt, MCH, NPY, POMC, etc.) (Adamantidis and de Lecea, 2009). This approach opens new perspectives with regards to the role of the hypothalamus in the regulation of motivated behaviors. Although MCH, CART or NPY have been demonstrated modulators drug seeking behaviors (DiLeone et al., 2003; Thiele et al., 2004; Vicentic and Jones, 2007; Pissios et al., 2008; Jaworski et al., 2008; Chung et al., 2009), the impact of these cross-regulated intra-hypothalamic circuitries on motivation and reward seeking remains poorly understood. However, recent reports have established novel interactions between these hypothalamic systems. MCH and NPY, for instance, may exert a unique inhibitory influence on hypocretin/orexin signaling as a way to fine-tune the output of the LH (Rao al., 2009; Fu et al., 2004), and as a consequence, may work synergistically with Hcrt to maintain various levels of arousal required in different goal-oriented behaviors. Similarly, CART and Hcrt have been proposed to act synergistically in a reinstatement model for ethanol seeking (Dayas et al., 2007).

In sum, any neuronal cell type, in the LH and in other brain areas, might be selectively activated using the newly developed optogenetic methods, and this novel approach might potentially offer new ways of probing neural circuits regulating the brain reward function with unprecedented cellular specificity and temporal resolution, before, during and after the acquisition of drug related behaviors. Two recent reports have demonstrated the relevance of optogenetic stimulation to manipulate neuronal activity *in vitro* and *in vivo* using a fiber optic-based system to deliver light into the brain of freely moving mice. A first study established that Hcrt neurons are sufficient for increasing the probability of sleep to wake transitions (Adamantidis et al., 2007). A second approach used optogenetic tools to selectively stimulate VTA dopaminergic neuron action potential firing in freely behaving mice, and showed that phasic dopaminergic activity, and dopamine release in the nucleus accumbens, is sufficient to mediate behavioral conditioning (Tsai et al., 2009). Similar approaches should contribute to unveil the role of Hcrt in driving goal-oriented behaviors and eliciting motivation for reward seeking.

Discussion and hypotheses

Growing evidence suggests the implication of the Hcrt system in many different classes of drug reward, including cocaine, morphine, nicotine, and ethanol. As mentioned above, whereas blockade of Hcrtr-1 does not seem to reduce psychostimulant consumption, blocking the Hcrt system reduces both nicotine and alcohol intake in rats. Importantly, there is a consensus on the role of the Hcrt system in conditioned responding for drug-associated stimuli (context or cues), which means Hcrts may be critically involved in addiction disease, most likely in stress- and stimulus-induced drug relapse. However, the question remains as to how a system that would be normally involved in the regulation of goal-oriented behaviors may promote a pathological state that elicits compulsive craving and relapse to drug seeking after a period of protracted abstinence. This observation raises again the question of how drugs of abuse alter neural circuitries and normal behaviors (Hyman, 2005).

Hcrts and the urge for reward seeking: an allostatic adaptation in basic needs

A recent report suggested an essential role of the Hcrt system in mediating reduced depression-like symptoms induced by short-term calorie restriction (Lutter et al., 2008). Briefly, it is proposed that, in contrast to chronic calorie restriction that results in depression- and anxiety-like behaviors in rats (Jahng et al. 2007), short-term calorie restriction promotes increased arousal, increased locomotor activity and decreased anxiety-like behaviors that could be attributed to the activation of the Hcrt system; an antidepressant-like response that would be however lost after chronic activation of the Hcrt system due to a downregulated expression of prepro-Hcrt mRNA in the LH (Lutter et al., 2008). In line with this interpretation, one can wonder what kind of debilitating long term effect could be associated with excessive activation of the Hcrt system upon drug intoxication. Indeed, considering that the Hcrt system receives sensory stimuli and relays them to brainstem nuclei, the HPA axis and to arousal- and stress-related forebrain regions (Tsujino and Sakurai, 2009), what could happen upon chronic drug intoxication? At cessation of drug consumption, the Hcrt system may act as an alarm signal that would prepare the organism for withdrawal and face the consequences on energy and fluid homoeostasis (such as starvation activates the Hcrts and elicits food seeking to prevent caloric restriction).This assumption is in line with the diminished signs of precipitated opiate withdrawal displayed by mutant mice deficient in Hcrt (Georgescu et al., 2003) and the recent observation according to which Hcrt mediates the expression of precipitated morphine withdrawal in C57BL/6J mice (Sharf et al., 2008). We suggest that upon chronic drug exposure (and concomitant recurrent withdrawals), the Hcrt system may contribute to elicit allostasis within the brain stress and brain reward mechanisms (Leri et al., 2009; Zhou et al., 2006). 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 (Mc Ewen and Wingfield, 2003; Koob and Le Moal, 2001). It is now well accepted that, depending on physiological needs (hunger, thirst), Hcrts elicit appropriate level of alertness to engage exploratory behaviors and strengthen motivation for food seeking. We consider that chronic drug intoxication may induce change in basic needs priorities, and that the Hcrts may contribute (as a means to maintain stability of the internal milieu in case of dependence) to a particularly vulnerable state of the brain

that may trigger the urge for drug seeking and drug taking, even long after last consumption and withdrawal (Boutrel and de Lecea, 2008).

Hcrts and sustained attention: an allostatic regulation of goal-directed behaviors

Although it remains unclear whether Hcrt fibers synapse onto DA neurons within the VTA, and despite the only detection of Hcrtr-2 in the VTA (Carter et al., 2009), the Hcrtr-1 antagonist SB-334867 is considered to be efficient for reducing reward seeking when injected directly into the VTA (Aston-Jones et al., 2009). As mentioned above, it is quite difficult to interpret the Hcrt-induced reinstatement of cocaine seeking through induction of DA release since i.c.v infusion of Hcrt does not lower, but elevates ICSS thresholds. Further studies are needed to dissect brain mechanisms involved in Hcrt-induced reinstatement of reward seeking, and the precise role of Hcrts in operant conditioning.

This review pointed out the role of Hcrts in attentional processes, and it is noteworthy to question whether the Hcrt system is directly involved in the regulation of motivated behaviors, or acts primarily to optimize the processing of signals in attention-demanding contexts. This interpretation questions the most recent observations claiming a role for Hcrt in cue- and context-driven cocaine seeking (Smith et al., 2009a,b), especially since the high doses of the Hcrt-1 receptor antagonist SB 334867 are known to induce sedative effects and attention deficits (Rodgers et al., 2001; Boschen et al., 2009).

Recent evidence using functional brain imaging suggests that anticipation of financial gains activates the nucleus accumbens (a brain area activated upon risk-seeking strategies) and correlates with self-reported positive arousal. In contrast, excessive prices can elicit insula activation (a brain area activated upon risk-averse strategies) and mPFC deactivation, and correlates with self-reported negative arousal (Knutson et al., 2001; Paulus et al., 2003; Paulus and Stein, 2006; Knutson et al., 2007). Since Hcrt fibers have been shown to innervate both the NAcc (Baldo et al., 2003) and the insula (Hollander et al., 2008), it is tempting to speculate that Hcrts may contribute to define behavioral strategies by optimizing the processing of environmental signals in attention-demanding tasks with regard to past experience. Hence, the Hcrt system may enhance cognitive arousal and attentional performance for improving prediction making, and drive sustained attention for achieving the goal-oriented behavior whatever the context is: reward seeking or punishment avoidance (see Berridge et al., 2009). In line with this interpretation, a recent study established that cues previously paired with cocaine consumption elicited a significant increase in cFos-positive Hcrt neurons compared to cues previously paired with sweetened condensed milk. Further, following the extinction, the number of Fos-positive Hcrt cells was decreased in cocaine rats compared to drug naïve ones and those exposed to the sweetened condensed milk, suggesting a decreased activity in Hcrt neurons of rats with a history of drug abuse. Strikingly, the Hcrtr-1 antagonist SB334867 was shown to dose-dependently reduce cue-induced cocaine seeking at lower doses (starting at 3 mg/kg) than those used for preventing cue-induced sweetened condensed milk seeking (Martin-Fardon et al., 2009). Again, chronic drug intoxication may induce changes in basic needs priorities, and the Hcrt system may be part of a common mechanism for adapting and/or ranking priorities and eliciting appropriate

levels of alertness to drive attention processes and trigger goal-directed behaviors according to these new priorities.

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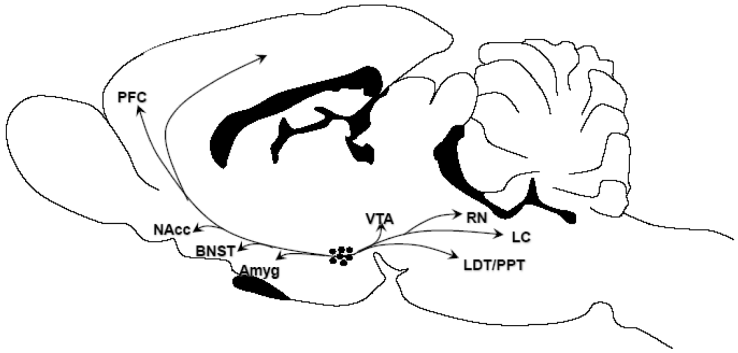

Figure.

Hypocretin producing neurons (dots) are restricted to the lateral hypothalamus and project throughout the brain, in particular to brain regions involved in arousal 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 Coeruleus; LDT/PPT: Laterodorsal tegmentum and Pedunculo Pontine Tegmentum