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## Addiction and arousal: the hypocretin connection

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### Abstract

The hypocretins, also known as orexins, are two neuropeptides now commonly described as critical components to maintain and regulate the stability of arousal. Several lines of evidence have raised the hypothesis that hypocretin-producing neurons are part of the circuitries that mediate the hypothalamic response to acute stress. Intracerebral administration of hypocretin leads to a dose related reinstatement of drug and food seeking behaviors. Furthermore, stress-induced reinstatement can be blocked with hypocretin receptor 1 antagonism. These results, together with recent data showing that hypocretin is critically involved in cocaine sensitization through the recruitment of NMDA receptors in the ventral tegmental area, strongly suggest that activation of hypocretin neurons play a critical role in the development of the addiction process. The activity of hypocretin neurons may affect addictive behavior by contributing to brain sensitization or by modulating the brain reward system. Hypocretinergic cells, in coordination with brain stress systems may lead to a vulnerable state that facilitates the resumption of drug seeking behavior. Hence, the hypocretinergic system is a new drug target that may be used to prevent relapse of drug seeking.

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The hypocretins (also known as orexins) are two neuropeptides, hypocretin-1 (hcrt-1) and hypocretin-2 (hcrt-2), derived from the same precursor gene (prohypocretin) produced in a few thousand neurons localized in the perifornical area of the lateral hypothalamus. [1,2]. Hypocretin producing neurons project throughout the brain and especially to areas involved in energy homeostasis, arousal and brain reward. The distribution of hypocretin terminals is consistent with the partially overlapping but complementary distributions of the two hypocretin receptors [3,4]. Afferents to hypocretin neurons project from the basal forebrain, bed nucleus of the stria terminalis, lateral septum, preoptic area, and posterior hypothalamus [5].

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Evidence from multiple experiments indicate that hypocretin neurons in the lateral hypothalamus receive inputs from diverse sensory and limbic systems to provide a coherent output that results in the stability of the states of vigilance [6-8]

### The hypocretins are critical for the maintenance of arousal

Narcolepsy is a neurological disorder characterized by excessive daytime sleepiness and cataplexy attacks. Narcoleptic patients also exhibit sleep onset REM direct transition from wakefulness to rapid-eye movement (REM) sleep [9], which are suggestive of the inability to control the boundaries between vigilance states. The link between hypocretins and narcolepsy was evidenced when positional cloning revealed that a mutation in the canine hypocretin receptor 2 segregated with a narcoleptic phenotype in dogs [10]. Furthermore, pre-prohypocretin knockout mice show periods of cataplexy-like attacks and sudden onset of REM sleep [11,12]. This narcolepsy-like phenotype is also observed in transgenic mice and rats with selective postnatal degeneration of hypocretin-expressing neurons [13,14] and in the narcolepsy condition can be rescued either by pharmacological or genetic means [15]. Also, human narcoleptic brains are practically devoid of hypocretin-producing neurons [16,17]. These data unequivocally demonstrate that narcolepsy is a disease of the hypocretinergic system.

Studies in transgenic animals have shown that, in addition to their key role in the regulation of transitions between vigilance states, the hypocretins may be involved in linking information about nutritional and metabolic state and promotion of arousal. Thus, while most mammals respond to reduced food availability by becoming more wakeful and active, transgenic mice depleted of hypocretin neurons fail to respond to fasting with increased activity and arousal [18]. Recent data also indicate that the hypocretinergic system receives input from the brain circuitry that modulates stress.

### The hypocretinergic system may be a component of the stress response

Behavioral arousal is a key component of the stress response. A well-characterized physiological response to stress affects the hypothalamo-pituitary-adrenal (HPA) axis. Upon stress stimulus, synthesis of the corticotropin-releasing factor (CRF) is induced in the paraventricular nucleus of the hypothalamus. Stimulation of the pituitary corticotroph cells by CRF stimulates the production of the adrenocorticotrophic hormone (ACTH). The primary target of ACTH is the adrenal gland from which ACTH stimulates the release of glucocorticoids, which in turn provide a feedback loop to the pituitary and hypothalamus to stop the response to stressful stimuli [19].

As discussed above, hypocretin-containing neurons are critical components of the circuitry that modulates and sets the arousal threshold [8]. Thus, one can expect a role for the hypocretinergic system in the “hyperarousal” state that characterizes stress. Indeed, icv injection of hcrt-1 increases food consumption [20-23], locomotor activity [24-26] and body temperature [27,28]. Moreover, central administration of hcrt-1 stimulates gastric acid secretion, increases arterial blood pressure, heart rate, cerebral blood flow and sympathetic nerve activity [29,30], and mice deficient in prepro hcrt display low sympathetic tone. [31].

Increasing evidence suggests that hypocretin neurons receive afferents from neurons belonging to the brain stress system. CRF-containing terminals form synapses onto hypocretin neurons [32]. Intracellular recordings of hcrt neurons, identified by EGFP staining in hypothalamic slices from orexin/EGFP indicate that CRF directly depolarizes hypocretinergic cells [32]. This effect is likely mediated through CRFR1 since astressin, a CRF-R1 selective antagonist, blocked the CRF-induced depolarization of hypocretin neurons. The functional significance of the CRF-hypocretins interaction was tested during acute stress such as restraint or footshock stress. Restraint stress dramatically increases prepro-hypocretin mRNA steady state concentration [33]. Both acute stress paradigms induce c-Fos immunoreactivity in hypocretin-producing neurons of wild type mice. However, activation of c-Fos in hypocretinergic neurons after footshock and restraint stress was decreased in mice deficient in CRF-R1 [32]. These results suggest that the stress-induced activation of hypocretinergic neurons occurs through the CRF-R1 receptor. The hypocretinergic system may be a component of the central response to acute stress activated by CRF (Figure 2).

Hypocretin neurons are reciprocally connected with NPY-containing neurons [34], another peptidergic system involved in the multiple responses to acute stress. [35]. Interestingly, icv administration of NPY increases sedation [36] and has anxiolytic activity in response to some stimuli [37-39]. NPY potently hyperpolarizes hypocretin neurons *in vitro* [40]. It is thus possible that some of the behavioral effects of NPY are mediated by inhibition of the hypocretinergic system.

This circuitry between CRF, hypocretin and NPY may have significant relevance in multiple physiological and pathological situations, and in particular in hyperaroused states associated with motivation and addiction.

## The hypocretins and addiction

The relationship between stress and addiction is well established and the extended amygdala has been shown to play a key role in mediating both positive and negative reinforcement associated with drug addiction [41-43]. The extended amygdala is comprised of the medial subregion of the nucleus accumbens (shell of the nucleus accumbens), the bed nucleus of the stria terminalis, and the central nucleus of the amygdala. This structure receives numerous afferents from limbic regions, such as the basolateral amygdala and hippocampus, and sends not only afferents to the medial part of the ventral pallidum but also to the lateral hypothalamus, thus further defining the specific brain areas that interface classical limbic structures with the extrapyramidal motor system. Thus, the extended amygdala provides a connection for the basal forebrain to the classical reward systems of the lateral hypothalamus via the medial forebrain bundle reward system [44,45].

Interestingly, the hypocretinergic system projects to all the major components of the extended amygdala, namely, the central amygdala, the shell of the nucleus accumbens (NAcc) and the bed nucleus of the stria terminalis (BNST) (Figure 2) [4,46]. Since hypocretins have been shown to be involved in the GABAergic modulation of the mesolimbic dopamine system, [47-49], this peptidergic system fulfills all the

neuroanatomical and functional criteria to modulate critical connections that regulate both positive- and negative-reinforcing properties of drugs of abuse.

Several lines of evidence suggest that hypocretins are involved in the modulation of the brain reward function. First, both lesions experiments and the intracranial self-stimulation (ICSS) paradigm have suggested an important role of the lateral hypothalamus in reward [50,51]. Compared to other brain regions, ICSS in the LH, also called LHSS, is by far the most potent [52]. Secondly, maintenance of energy homeostasis requires the coordination of systems that regulate feeding, body temperature, autonomic and endocrine functions with those that modulate an appropriate state of arousal and motivation. The close interaction between the CRF and the hypocretin peptidergic systems [32,53-55], places hypocretin neurons as a key system in the integration of emotional stimuli.

To directly test whether the hypocretins were involved in the acquisition of drug consumption, we infused 0.2-1.5 nmoles of hcrt-1 into the brains of rats trained to self administer cocaine (0.25 mg/kg/infusion). No differences were observed compared with saline-treated rats after single or repeated injections of the peptide, at different periods of the circadian cycle, and at different exposure times to cocaine, using a fixed- or a progressive-ratio schedule of reinforcement [56].

Thus, we concluded that hypocretin did not modulate cocaine intake in rats. However, we showed that intracerebroventricular (icv) infusions of hypocretin-1 led to a dose-related reinstatement of a previously extinguished cocaine seeking behavior. We have then demonstrated that the same dose of hcrt-1 elevated intracranial self-stimulation (ICSS) thresholds, indicating a decrease in excitability of brain reward systems. This effect was in sharp contrast to the well known 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 was similar to that observed after icv infusion of CRF [57] or after drug withdrawal [58,59]. These data provide strong evidence suggesting that hcrt-1 reinstated cocaine seeking by mechanisms different from increased dopamine release only [60]. Indeed, the blockade of hcrt-induced reinstatement of cocaine seeking by CRF/NA antagonism rather suggests that hypocretin and stress systems may closely interact to regulate cocaine seeking behavior. This hypothesis was later confirmed using a hcrt-1 antagonist, SB 334867, to prevent footshock-induced reinstatement of a previously extinguished cocaine seeking behavior. Overall, these findings identify the hcrt system as a new mechanism by which stress could influence relapse to drug seeking and drug taking. Emerging evidence suggests long-lasting cocaine-induced neuroadaptations that give stress input access to mesolimbic circuitry and that predisposes stressed animals to relapse to cocaine seeking. CRF was shown to induce glutamate release in the VTA of cocaine-experienced but not in cocaine naïve-rats [61]. Interestingly, hypocretins have been shown to act synergistically with glutamatergic afferents to depolarize both cholinergic neurons in the LDT [62] and dopaminergic neurons in the VTA [63]. Further, hypocretin has been shown to critically contribute to cocaine sensitization through the recruitment of NMDA receptors in the VTA [64]. Taken together, the result suggests that hypocretins, in coordination with CRF, could contribute to glutamate release facilitation which ultimately

could lead to arousal/motivational systems activation, including both noradrenaline and dopamine systems. A chronic activation of such brain systems could lead to an allostatic state of brain reward system, or hedonic set point (see [65]), and could underlie vulnerability to relapse for drug seeking after a period of protracted abstinence and/or detoxification.

We propose that the Hcrt system (receiving sensory stimuli and relaying them to brainstem nuclei, the HPA axis and also to arousal- and stress-related forebrain regions) could be activated by chronic drug intoxication. At cessation of drug presentation, the hypocretin system may act as an alarm signal that would prepare the organism for withdrawal and its consequences on energy and fluid homoeostasis (such as starvation activates the hcrt to face its consequences on metabolic/caloric needs). In this context, leptin, which hyperpolarizes hypocretin neurons, also attenuates fasting-induced heroin-seeking behavior [66], and mutant mice deficient in Hcrt display diminished signs of precipitated opiate withdrawal [67]. The main question remains whether or not a chronically activated hypocretin system upon chronic drug exposure (and recurrent withdrawals) may elicit allostasis within the brain reward mechanisms as a means to maintain stability in the face of chronic demand, and ultimately lead to a particularly vulnerable state of the brain given that hypocretin priming by stress events may facilitate the resumption of drug seeking behavior even months or years after detoxification. Understanding the alterations in such fundamental homeostatic systems within the brain may be the key to prevent a variety of pathophysiological dysfunctions including affective and addictive disorders [68].

As a conclusion, we propose that the hypocretinergic system could play a relevant role in both homeostatic (upon stress stimuli as well as during drug withdrawal) and allostatic regulation of physiological functions related to arousal, stress and motivation (in the latter case, after a prolonged period of drug intoxication and/or during protracted abstinence). We therefore suggest that hypocretin may represent a target for preventing drug craving and vulnerability to relapse.

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