Hypocretin/Orexin Receptor Antagonism and the Promise of Anticraving medications: Myth or Panacea?

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Abstract

A general consensus acknowledges that drug consumption (including alcohol, tobacco and illicit drugs) constitutes the leading cause of preventable death worldwide. An even more pessimistic observation suggests that drug abuse is not only a major cause of mortality but also it significantly deteriorates the quality of life of individuals suffering from the long-term debilitating effect of the disease. Despite the large body of evidence delineating the cellular and molecular adaptations induced by chronic drug consumption, the brain mechanisms responsible for drug craving and relapse remain insufficiently understood, and even the most recent developments in the field have not brought significant improvement in the management of drug dependence. Here, we review recent evidence demonstrating an important role for the hypocretin (orexin) neuropeptide system in regulating drug reward, and notably in preventing drug relapse. We then propose to discuss why disrupting the hypocretin system may serve as an anticraving medication since during the transition to addiction, the hypocretin system, normally orchestrating the appropriate levels of alertness required for the execution of goal-oriented behaviors, may be compromised and contribute to the pathological state by eliciting compulsive drug craving. Finally, we question the undesirable effects associated with a pharmacologically impaired hypocretin system, which may limit the applicability of the anticipated anticraving action of such a medication.

Introduction

“When it comes to kicking a drug habit, going through withdrawal is the easy part. The cold-turkey alcoholic shaking with delirium tremens might not agree, but only after the body detoxifies does the real challenge begin: staying clean. Ex-addicts with the strongest resolve-and plenty of external motivation in the form of frayed relationships, probationary jobs, or incipient lung cancer-struggle to resist cravings and are susceptible to relapse even years after their last dose” [1].

Quitting a drug habit is not as simple as it may seem and the journey to a drug-free life is nothing but an endless personal combat to resist temptations once detoxified. This inability to control drug taking is thought to be a complex disease of the brain that strikes the most vulnerable individuals and worsens with recurring drug intoxication. The use of psychoactive substances causes significant health and social problems for the people who use them, and also for their relatives. The World Health Organization (WHO) recently estimated that over one billion people were tobacco users and that alcohol disorders affected about 80 million people [2]. In an initial estimate of factors responsible for the global burden of disease, tobacco, alcohol and illicit drugs contributed together to 12.6% of all deaths worldwide (up to 19.6% in high income countries) in the year 2000. Tobacco use and alcohol consumption are ranked respectively the second and the eighth leading risk factors of death, responsible for 5.1 and 2.3 millions of death worldwide each year. In the U.S., over 400,000 people die every year from tobacco-related disease and about 85,000 people die each year from the consequences of alcohol consumption, including alcohol-related illnesses and accident, whereas illegal drug use contributes to 17,000 deaths [3]. One of the differences between the main categories of psychoactive substances is the fact that they inflict their disease burden on different age groups.

Whereas the illicit drug use results in the heaviest burden of mortality over 400,000 people die every year from tobacco-related disease and 200,000 from alcohol consumption, the global burden of disease in 2004 was due to cocaine and opioid use, with the social cost of illicit substance use being around 2% of Gross Domestic Product in those countries for which it has been measured. Besides this unacceptable human cost, Kerry Smith recently reported that addictive disorders cost Europe €65.7 billion [5]. It is also estimated that over 11% of US federal and state government budgets ($374 billion in 2005) are spent dealing with the consequences of tobacco, alcohol, and other substance use, abuse, and dependence. Finally, without alleviating their negative impact on health, it is important to note that WHO estimated that only 0.7% of the global burden of disease in 2004 was due to cocaine and opioid use, with the social cost of illicit substance use being around 2% of Gross Domestic Product in those countries for which it has been measured. In brief, the treatment of drug addiction should be a priority in public health policy, and remained a challenge for both fundamental and clinical investigations.

In this context, there is a general consensus accepting that the reinforcing properties of drugs of abuse arise, at least in part, from a potentiation of dopaminergic neurotransmission within...
the mesocorticolimbic circuit. However, this consensus has never brought any effective treatment for alleviating signs of drug addiction. Meanwhile, emerging data suggests that neurotransmitters other than dopamine may also play important roles in the motivational properties of drugs [6]. The aim of this review is to highlight some of the recent evidence demonstrating an important role for the hypocretin (orexin) neuropeptide system in regulating the reinforcing properties of most of the categories of drugs of abuse.

The Hypocretin/Orexin system in brief

The hypocretins (Hcrt, also known as orexins) are two neuropeptides, hypocretin-1/orexin-A and hypocretin-2/orexin-B, derived from the same precursor gene produced in a few thousand neurons localized in the perifornical area (PFA) of the lateral hypothalamus (LH) [7,8]. Hypocretin-containing neurons arise in the LH area and project widely in the brain with a dense innervation of anatomical sites involved in regulating arousal, motivation and stress states, where the released peptides bind to two G-coupled receptors, Hypocretin receptor 1 (Hcrtr-1) and Hcrtr-2. Their interaction with autonomic, neuroendocrine and neuroregulatory systems strongly suggests that they act as neuromodulators in a wide variety of neural circuits [9]. In complement of a wide innervation of various neural circuits, the hypocretinergic system projects to all the major components of the extended amygdale [10], a brain region known to connect the basal forebrain to the classical reward systems of the LH via the medial forebrain bundle reward system. Hence, the hypocretinergic system fulfils both neuroanatomical and functional criteria to modulate critical connections that regulate both positive- and negative-reinforcing properties of drugs of abuse. However, the first compelling evidence supporting a physiological role for this peptidergic system established a fundamental role of the Hcrt in the regulation of arousal. A key contribution in the etiology of narcolepsy was provided by several studies linking the Hcrt system to this disease. Genetic narcoleptic dogs with a mutation in the Hcrt receptor 2 gene [11], and mice with a null mutation of the preprohypocretin gene [12] showed symptoms of narcolepsy, suggesting that impairment of the Hcrt system may underlie the syndrome of human narcolepsy. This assumption was later confirmed with the demonstration that human narcoleptic patients exhibit a drastic reduction (85%-95%) in Hcrt-1 peptide in the cerebrospinal fluid and in the number of Hcrt neurons leading to the hypothesis that narcolepsy could be related to the ongoing loss of Hcrt neurons [13-15]. In the current models, the Hcrt stabilize the firing of brainstem neurons that promote wakefulness and Rapid Eye Movement (REM) sleep and exert a strong and direct excitatory effect on the cholinergic neurons in the basal forebrain that contribute to cortical arousal [9]. In conclusion, the Hcrt system may be considered as a key regulator that integrates sensory inputs and orchestrates the arousal threshold [16-18]. The fact that any kind of disruption or hypocretin transmission may cause destabilization of the boundaries between sleep states, similar to those found in narcolepsy, may pose quite a serious concern with regards to anti-Hcrt medication.

Evidence for a role of the Hypocretin/Orexin system in drug reward

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 [19]. This observation was later confirmed with a pharmacological blockade of the Hcrt transmission in C57BL/6J mice [20]. Our group, for the first time, suggested that Hcrt could play a key role in the modulation of brain reward function [21]. But the first compelling evidence reported that activation of LH Hcrt neurons (or infusion of Hcrt-1 peptide directly into the ventral tegmental area, VTA) reinstated an extinguished preference for an environment repeatedly paired with drug reward in rats, and that a morphine priming injection activated LH Hcrt neurons of extinguished rats [22]. Further observations later confirmed the involvement of the Hcrt system in drug reward.

With regards to cocaine, it has been established that daily pretreatment with the Hcrtr-1 antagonist SB334867 prevented cocaine sensitization [23] but did not block daily cocaine intake in a self-administration procedure [24]. In contrast, a single injection of the Hcrtr-1 antagonist SB334867 was shown to prevent both Hcrt-, footshock- and cue-induced reinstatement of a previously extinguished cocaine seeking behavior [24-26], without however reducing cocaine consumption in a fixed ratio schedule of reinforcement [24-26]. Hcrt transmission may therefore selectively regulate “relapse” like behaviors in abstinent rats, but may not play any critical role in the reinforcing effects of the drug that maintain ongoing drug-taking behavior. This assumption remains debatable though, since data were quite controversial when rats were trained to self-administer cocaine using a progressive ratio schedule of reinforcement, a procedure during which the number of lever presses required to earn one reward increases gradually within the session. Indeed, two studies reported that the final ratio (i.e. number of infusions) obtained by rats before termination of the session remained unchanged after infusion of the peptide or the receptor antagonist [25,26], whereas two other studies claimed that blockade of Hcrtr-1 (with the Hcrtr-1 antagonist SB334867) reduced the performance to self-administer cocaine in rats [27,28]. Thus, an alternative suggestion is that Hcrt transmission may be necessary to maintain cocaine-taking behavior when high levels of effort are required to obtain the drug, but not when the drug is readily available [29].

In addition to psychomotor stimulants, Hcrt transmission also plays an important role in regulating seeking behaviors for opiates, nicotine and alcohol. Indeed, recent reports demonstrated (i) the ability of the Hcrtr-1 antagonist SB334867 to decrease both alcohol and nicotine self-administration behaviors [30-37], (ii) administration of Hcrt directly into the paraventricular nucleus or in the LH increases ethanol-drinking in rats without affecting food and water intake [38], (iii) reinstatement of extinguished alcohol seeking is associated with activation of Hcrt neurons [39,40] and (iii) Hcrt signaling is essential for the expression of nicotine withdrawal [41]. Interestingly, recent clinical evidence suggests an involvement of the Hcrt system in the affective dysregulation observed in alcohol dependent patients during alcohol withdrawal [42,43] and in abstinent smokers during nicotine withdrawal [44], thus confirming the potential key role of the Hcrt system in drug withdrawal.

The respective roles of Hcrt-1 and Hcrt-2 remain controversial though. A recent report claimed the effectiveness of the Hcrt-2 antagonist [N(1)-797049 in reducing the reinforcing effects of ethanol, in particular in dose-dependently decreasing ethanol self-administration without affecting saccharine consumption in rats [45]. Unexpectedly, this report claiming that treatment with [N(1)-797049 (10 mg/kg, sc) attenuated the acquisition, expression, and reinstatement of ethanol conditioned place preference and ethanol-induced hyperactivity in mice, also claimed that the Hcrt r-1 antagonist SB-408124 (3, 10 and 30 mg/kg, sc) did not have any effect in these procedures [45], whereas the studies investigating the effect of SB 334867 all converged in supporting that Hcrtr-1 receptor antagonism decreases ethanol reward. A large consensus remained however on the
role of both Hcrt receptors in preventing cue-induced reinstatement of previously extinguished alcohol-drinking behavior [30,45]. 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 [19,20] as well as the absence of preference for a compartment previously paired with morphine administration in Hcrt-deficient mice [46] rather suggest a real potential for Hcrt in the regulation of opiates seeking and taking behaviors.

Concordant observations point to a role for Hcrt-1 in driving drug seeking, in particular cocaine, through activation of the mesolimbic dopamine system. Hcrt-1 peptide has been shown to be critically involved in cocaine sensitization through the recruitment of N-Methyl-D-Aspartate (NMDA) receptors in the VTA [23]. Hcrt-1 peptide administered into the ventral tegmental area was claimed to enhance dopamine responses to cocaine and promote cocaine self-administration [47] whereas administration of the Hcrt-1 antagonist SB 334867 attenuated cocaine-induced enhancement of dopamine signalling [27]. In line with this latter observation, other reports claimed that Hcrt receptors antagonism reduced amphetamine-evoked dopamine outflow in the shell of the nucleus accumbens (NAcc) and decreased the expression of both cocaine and amphetamine conditioned reward and sensitization [48-50].

Meanwhile, 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 [25]. 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 intracerebroventricular (i.c.v) infusion of corticotropin-releasing factor (CRF) [51] or after drug withdrawal [52]. Hence, this observation provides strong evidence suggesting that Hcrt-1 reinstates cocaine seeking by mechanisms different from increased dopamine release. In line with this observation, recent evidence suggests that intra-VTA or i.c.v administration of Hcrt-1 exerts its threshold-increasing effect via subsequent activation of the CRF system [53].

Hypocretin and the urge for reward seeking: an allocistic adaptation in basic needs

It is quite striking to note that growing evidence demonstrates 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 Hcrt-1 does not seem to reduce psychostimulant consumption, it is quite clear that 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 Hcrt may be critically implicated in addiction disease, most likely in stress-and stimulus-induced drug relapse [54].

However, a key question remains unanswered: how a system, that would be normally involved in the regulation of hyperaroused states in accordance with the elaboration of goal-oriented behaviors, may promote a pathological state that elicits compulsive craving and relapse to drug seeking after a period of protracted abstinence.

A recent report suggested that, in contrast to chronic calorie restriction that results in depression- and anxiety-like behaviors in rats [55], short-term calorie restriction would promote increased arousal, increased locomotor activity and decreased anxiety-like behaviors that could be attributed to the activation of the Hcrt system. This antidepressant-like response would be lost after chronic calorie restriction due to a downregulated expression of prepro-Hcrt mRNA in the LH [56]. Thus, in healthy physiological conditions, the Hcrt system may contribute to a resilient-like state by reducing depression-like symptoms induced by short-term calorie restriction, whereas a compromised Hcrt system upon chronic calorie restriction may contribute to worsen signs of anxiety and depression. Our idea is that a similar adaptation may occur during chronic drug consumption (and the concomitant recurring drug withdrawals). Indeed, it is well accepted that Hcrt elicits appropriate levels of alertness to engage exploratory behaviors and strengthen motivation for food seeking depending on physiological needs (hunger, thirst). Similarly, 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 homeostasis (such as starvation) is activating the HcrtS and eliciting food seeking to prevent caloric restriction. This assumption is in line with the diminished signs of precipitated opiate withdrawal displayed by both mutant mice deficient in Hcrt [19] and C57BL/6 mice treated with a Hcrt-1 antagonist [20]. We thus consider that chronic drug intoxication may induce change in basic needs priorities, and that the Hcrt 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 [57]. A novel role would be assigned to the Hcrt system, no longer for fine tuning arousal and goal-directed behaviors in response to metabolic needs, but for eliciting the hyperaroused and motivated state, if not anxious-like state [58], required for optimizing drug seeking, in other words drug craving.

Since Hcrt fibers have been shown to innervate both the NAcc [59] and the insula [36], it is tempting to speculate that Hcrt 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 attention for improving prediction making, and drive sustained attention for achieving the goal-oriented behavior whatever the context is: reward seeking or punishment avoidance [60]. 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 Hcrt-1 antagonist SB334867 was shown to reduce cue-induced cocaine seeking at lower doses (starting at 3 mg/kg) than those used for preventing cue-induced sweetened condensed milk seeking [61]. Again, chronic drug intoxication may induce change 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.

Potential consequences of a pharmacological disruption of Hcrt transmission

With the accumulation of preclinical evidence demonstrating a role for Hcrt in the maintenance of arousal, several pharmaceutical
companies have developed Hcrt receptor antagonists for the treatment of insomnia. SB-334867 was the first Hcrt-1 antagonist developed by GlaxoSmithKline (GSK) in the late nineties and remains to date the most studied Hcrt-1 antagonist. Several other Hcrt-1 and Hcrt-2 antagonists, consensually called SORA for Single Orexin Receptor Antagonists, as well as ligands with similar affinity for both receptors, also called DORA for Dual Orexin Receptor Antagonists, have been developed then. Exhaustive reviews covering patent literature published between 1999 and 2009 have been recently issued [62,63]. But these technical reports focused mainly on the chemical properties of these compounds.Further therapeutic opportunities offered by Hcrt ligands have been recently examined, however these reviews of the literature cover essentially the pharmacology of sleep and arousal [64,65]. Very few compounds have entered clinical development. Actelion, in partnership with GSK, has been conducting Phase III studies with the DORA almorexant for the treatment of insomnia. Merck also reported that the DORA MK-4305 entered into Phase III development for treating insomnia. Nevertheless, it has not been yet reported any clinical investigations with one of these compounds for treating drug addiction. Thus far, little is known on the putative adverse effects of Hcrt receptor antagonists. Nevertheless, a rapid review of the available evidence allows us to raise a few concerns about the effects of a pharmacological disruption of the Hcrt transmission [65].

In addition to the prominent role of the Hcrt system in arousal stability, Hcrt have been suggested to play a key role in driving arousal and goal-oriented behaviors [57]. Briefly, compelling evidence has established a role for the Hcrt in enhancing cortical arousal and attention, particularly with regard to limbic and visceral states [66]. In particular, Hcrt cells were shown to discharge with maximal activity during exploratory behavior, which can be considered as sustained attention or alertness [67]. Confirming this idea, systemic or intracerebral administration of the Hcrt-1 antagonist SB 334867 has been shown to disrupt attention in rats [68]. In line with these preclinical reports, recent clinical observation reported that narcoleptic patients exhibited attention deficits that cannot be attributed to sleepiness only [69]. Disruption of Hcrt signaling might therefore constitute a risk for developing attention deficits and quite serious long-term debilitating effects.

Further, Hcrt neurons are sensitive to glucose, leptin, triglycerides and carbon dioxide concentrations. Nevertheless, Hcrt do not seem to be critical players in food intake behaviors, but rather adapt arousal and motivation levels to allow feeding and drinking behaviors [9]. Depending on physiological needs (hunger, thirst), Hcrt elicits appropriate level of arousal to engage exploratory and goal-oriented behaviors. This can ultimately strengthen motivation for palatable food and liquids [28,70,71] or lead to the reinstatement of a previously extinguished food seeking behavior in an operand conditioning paradigm [25,72]. Consistent with this possibility, the inhibitory effects of SB-334867 on consumption of a palatable reinforcer (high-fat chocolate food) were recently shown to be dependent upon the level of effort necessary to obtain the reinforcer [28]. Interestingly, intra-LH Hcrt-1 had the greatest effects at higher effort-requiring schedules, whereas Hcrt-1 signaling appeared to have little involvement in responding for high fat or sucrose pellets in low effort situations [28,70]. In line with this observation, recent findings using the Hcrt-1 antagonist SB-334867, Hcrt knockout mice and RNA interference-mediated knockdown of Hcrt have shown that Hcrt-1 plays an important role in motivation to respond for food reinforcement, supporting a role for Hcrt transmission in maintaining physiological levels of caloric intake [73]. Overall, these findings highlight the important role for Hcrt transmission in the reinforcing and conditioned rewarding effects for non-drug reinforcers in addition to drugs of abuse, and the motivation to seek drugs during periods of abstinence. Thus, disrupting the Hcrt system may represent serious concerns with regards to appetite regulation.

Besides, it seems that the Hcrt do not drive alertness elicited by physiological needs only, but in response to psychological needs as well. Indeed, concordant evidence has recently suggested that Hcrt may potentiate male sexual behavior in rats [74-78] 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 [79]. These observations are considered to reflect greater 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 [79]. Therefore, Hcrt may promote sexual arousal in both male and female rats. Interestingly, the main reinforcing behavior in females is considered to be maternal care. Not surprisingly, Hcrt-1 modulates maternal behavior in mice [80]. Hence, not only does Hcrt drive appropriate levels of alertness in response to thirst and hunger, but also 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. Again, this observation may raise quite a few concerns with regards to a long-term disruption of the Hcrt system.

Conclusion

The Hcrt system controls sleep and wakefulness through multiple interactions with brain structures involved in the regulation of emotion, reward, stress and energy homeostasis. It is now quite accepted that Hcrt elicit appropriate levels of arousal to engage exploratory and goal-oriented behaviors depending on physiological needs (hunger, thirst), which drives motivation for food and liquid seeking. Our hypothesis is that chronic drug intoxication may compromise these basic needs priorities, and that the Hcrt system may become “high jacked” for triggering drug-oriented behaviors according to these new priorities. This assumption is supported by a large body of evidence demonstrating a role for the Hcrt system in drug reward, particularly in “relapse-like” behaviors in abstinent rats. Further, converging data now suggest a role for Hcrt in the affective dysregulation observed in dependent patients during alcohol and nicotine withdrawal.

Still, it remains unclear whether Hcrt antagonism may offer a clinical opportunity for reducing alcohol and nicotine consumption in dependent patients. Unfortunately, it appears quite clear that disrupting the Hcrt system will not reduce cocaine or amphetamine intake. A large consensus remains though on the possibility to treat dependent patients with Hcrt receptor blockers for alleviating symptoms of drug dependence, notably the urge for drug seeking during protracted abstinence from most major drugs of abuse. As reviewed above, the beneficial effects of such a medication may be limited by some serious side effects among which sleepiness, decreased appetite, attention deficits and reduced libido. In conclusion there is considerable evidence that the Hcrt system is key to many aspects of reward seeking behaviour and thus could prove to be a useful target for controlling relapse for drugs of abuse. However the fundamental role of these systems in more basic aspects of homeostasis and non-drug reinforcement need to be carefully considered in order to ensure that unintentional adverse consequences are not presented.
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