

# Arousal and reward: a dichotomy in orexin function

Glenda C. Harris<sup>1</sup> and Gary Aston-Jones<sup>2</sup>

<sup>1</sup> Department of Psychiatry, University of Pennsylvania, Translational Research Labs/3403, 125 South 31st Street, Philadelphia, PA 19104, USA

<sup>2</sup> Department of Neurosciences, Medical University of South Carolina, 401 BSB, 173 Ashley Avenue, Charleston, SC 29425, USA

**The orexins (or hypocretins) are neuropeptide transmitters made exclusively in hypothalamic neurons that have extensive CNS projections. Previous studies reported that this system is most strongly associated with feeding, arousal and the maintenance of waking. We review here recent studies that reveal a novel and important role for the orexin/hypocretin neuronal system in reward processing and addiction. We propose that the current evidence indicates a dichotomy in orexin function, such that orexin neurons in the lateral hypothalamus regulate reward processing for both food and abused drugs, whereas those in the perifornical and dorsomedial hypothalamus regulate arousal and response to stress. Evidence also indicates roles for lateral hypothalamus orexin neurons and ventral tegmental orexin receptors in reward-based learning and memory.**

## Introduction

During the development of addiction, occasional recreational use of drugs can expand into compulsive uncontrollable abuse of drugs. The treatment of addictions to drugs such as heroin and cocaine often fails, and a high percentage of addicts relapse or return to drug use after periods of abstinence ranging from days to years [1–3]. Human studies have indicated that craving for drugs or relapse in abstinent addicts can be triggered by exposure to the drug, drug-associated environmental cues or stress [4]. This relapse behavior is robustly modeled in rodents and numerous studies have demonstrated that psychological or physical stress, presentation of cues previously associated with the drug, or administration of the drug itself can reinstate drug-seeking behavior, even in the absence of drug reward [4]. The neuroanatomical and neurochemical mechanisms associated with relapse have been intensively studied over the past 15 years [5], but a complete understanding of the process of relapse remains elusive and many gaps still linger in our knowledge of this subject. Recent data described in this review indicate that orexin systems have an important role in reward processing and drug relapse.

## Functions of orexins

The orexins (also named hypocretins) were described by two groups in 1998, and comprise two distinct peptides

(A and B, which are 33 and 28 amino acids in length, respectively) that have two distinct receptors [6,7]. Orexin-expressing neurons are predominantly located in the posterior hypothalamus and extend dorsally, medially and laterally from the fornix [8]. Although small in number, orexin neurons have extensive projections throughout CNS and affect a variety of homeostatic functions [9,10].

Recently, Harris *et al.* showed that orexin neurons in the lateral hypothalamus (LH) are activated by cues associated with rewards such as food or drugs, and that exogenous stimulation of LH orexin neurons reinstates extinguished drug-seeking behavior in rodents [11]. The LH has long been implicated in homeostatic regulation, and lesion and intracranial self-stimulation studies have revealed an important role for this area in feeding, arousal and reward [12–15].

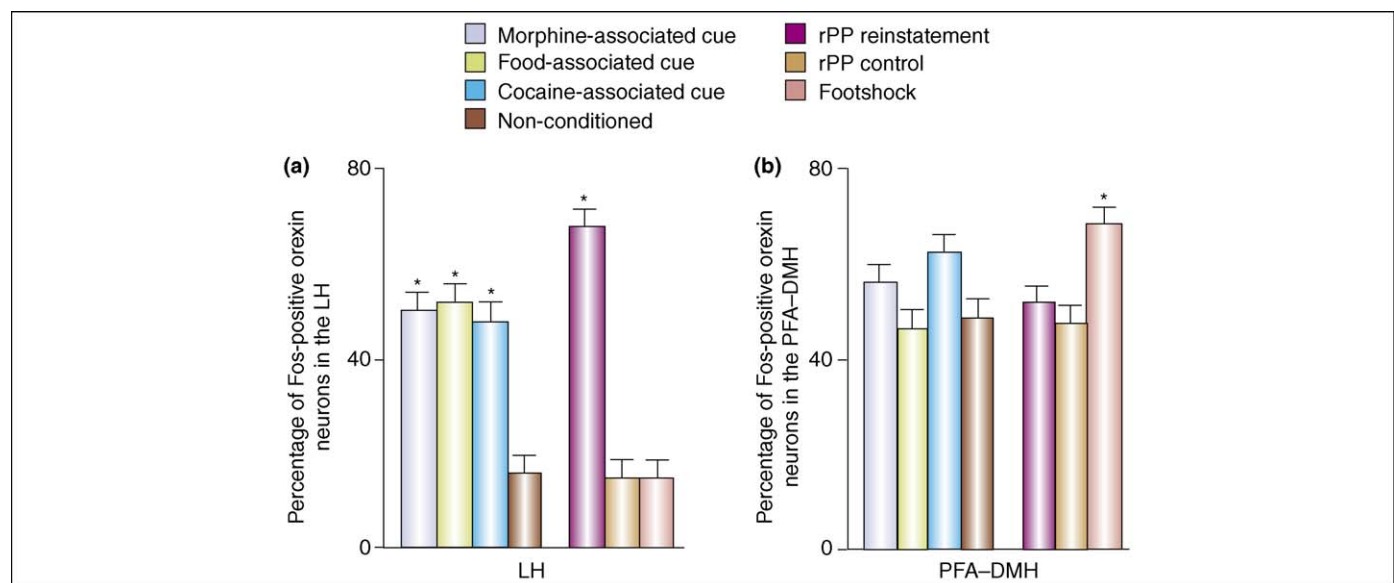
Intraventricular administration of orexin A mildly stimulates food intake (hence the name ‘orexin’ [7]). However, the orexin/hypocretin system is most well known for its role in the maintenance of arousal and waking [16,17]. Specifically, orexins are strongly implicated in the pathogenesis of narcolepsy, a chronic neurological disorder characterized by sudden, brief episodes of sleep that interrupt normal waking [10,16,17]. Mutations in the genes encoding either prepro-orexin or the OX2 receptor result in narcoleptic symptoms in mice and canines, respectively [18,19]. In addition, narcoleptic patients have low or undetectable orexin levels in cerebrospinal fluid, and few if any orexin neurons [16]. These results indicate that orexin neurons have roles in sleep–wake regulation, feeding and drug reward.

## Different populations of orexin neurons are involved in arousal versus reward

Narcoleptic patients are often treated using highly addictive amphetamine-like drugs [20] but they rarely become addicted to these drugs [21,22]. Furthermore, orexin knockout mice are less susceptible than wild-type animals to developing morphine dependence as measured by physical withdrawal responses [23]. This information, along with the aforementioned recent results of Harris *et al.* [11], indicates that orexins have functions in addition to feeding and arousal, and that they might have an important role in addiction.

Additional evidence leads us to propose that there is a functional dichotomy for orexin neurons, with different

Corresponding author: Aston-Jones, G. (astong@musc.edu).  
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**Figure 1.** Orexin neurons located in the lateral hypothalamus (LH) or perifornical and dorsomedial hypothalamic areas (PFA–DMH) show different patterns of Fos activation. **(a)** Percentages of LH orexin neurons that are doubly labeled for orexin and Fos following different stimuli. LH orexin neurons in conditioned animals expressed significantly more Fos in response to cues associated with morphine, cocaine or food during a test for conditioned place preference than those in non-conditioned animals. Reinstatement of extinguished morphine place preference occurred when rat pancreatic polypeptide (rPP), an agonist of Y4 neuropeptide Y receptors and a potent stimulator of orexin neurons, was microinjected into LH, but not when it was microinjected into areas surrounding LH (rPP control). Effective rPP microinjections significantly elevated Fos levels in LH orexin neurons, but not other orexin neurons. Exposure to footshock did not activate LH orexin neurons. **(b)** Percentages of PFA–DMH orexin neurons showing double labeling for orexin and Fos. PFA–DMH orexin neurons showed an elevation in Fos expression above baseline only after footshock and exposure to cocaine-associated cues. \* $P < 0.01$ . These data were previously described in Ref. [11].

groups of these cells involved in arousal and waking versus feeding and addiction. Specifically, we propose that orexin neurons located in perifornical and dorsomedial hypothalamic areas (PFA–DMH) are involved in arousal and waking, whereas those located in the LH are primarily involved in reward processing. This functional dichotomy is suggested by several previous studies. Estabrooke *et al.* [24] reported that activation of Fos in orexin neurons of the PFA–DMH shows diurnal changes consistent with a role in the production or maintenance of arousal; however, LH orexin neurons showed no such diurnal property. Fadel *et al.* [25] reported that anti-psychotic drugs that are associated with excessive weight gain preferentially activate orexin cells in the LH rather than the DMH, and that the amount of activation in LH orexin neurons correlates with weight gain.

The recent study by Harris *et al.* [11] provided additional evidence in favor of this functional dichotomy hypothesis, finding that orexin neurons in the LH, but not those in the PFA or DMH, are strongly involved in reward-related behaviors. These experiments used a two-chamber conditioned place-preference model in which one chamber is associated with drug or food reward through repeated pairings, whereas the other chamber is associated with no reward. Preference for reward is measured one day after conditioning by the amount of time animals spend in the reward-associated chamber minus the time they spend in the non-rewarded chamber, when given free access to both chambers. Cues previously conditioned with food or drug reward dramatically increased activity (as measured by Fos-like immunoreactivity) specifically within the LH orexin subpopulation, whereas Fos activation in PFA–DMH orexin neurons in response to these same cues was not markedly altered (Figure 1). In

addition, Fos activation in LH orexin neurons correlated strongly with the preference animals exhibited for the drug-paired or food-paired environment, whereas no relationship was seen between preference and Fos activation in PFA–DMH orexin neurons. Cocaine-associated cues produced a small increase in Fos activation in the PFA–DMH orexin cell populations. This effect of cocaine-associated cues might reflect arousal produced by cues conditioned with this psychostimulant.

Stimuli associated with abused drugs can powerfully drive relapse of drug taking in abstinent addicts. The response of LH orexin neurons to morphine- or cocaine-conditioned stimuli led us to speculate that activity in these cells might be involved in such relapse. This idea was tested by examining reinstatement of an extinguished preference for a drug-paired environment, a behavioral model of drug-seeking. Microinfusions of rat pancreatic polypeptide (rPP), a potent stimulator of orexin neurons [26], into the LH strongly reinstated an extinguished preference for a morphine-associated environment [11]. This reinstatement effect was completely blocked by prior systemic treatment with SB 334867, an antagonist of orexin A. Infusions of rPP outside the LH, or into the PFA–DMH, neither activated LH orexin neurons (Figure 1) nor reinstated morphine preference. Importantly, the reinstatement of morphine-seeking behavior by rPP administration into the LH was strongly correlated with the amount of Fos activation in LH orexin neurons ( $R = 0.99$ ,  $P < 0.01$ ). This effect might be mediated in part via the ventral tegmental area (VTA), because orexin administration directly into the VTA also reinstated an extinguished drug preference.

Taken together, these data indicate a strong role for LH orexin neurons in food and drug seeking behavior, whereas

PFA–DMH orexin neurons appear to be more involved in arousal.

### Role of orexin in stress and arousal

Stress also prominently stimulates drug relapse in abstinent addicts, an effect that is modeled in animal studies using footshock stress [27]. Importantly, Harris *et al.* showed that footshock at levels that produce reinstatement of drug-seeking behavior [27] activates orexin neurons in PFA–DMH but not those in the LH [11] (Figure 1). This finding is consistent with other reports showing that footshock, restraint or cold-exposure stress [28,29] all increase Fos expression in PFA orexin neurons.

Further support for this view is found in a recent report that links orexin with the corticotropin release factor (CRF) system and stress-induced drug relapse. Boutrel *et al.* [30] found that intracerebroventricular (icv) infusion of orexin produces a dose-related reinstatement of extinguished cocaine self-administration in rats, an effect that was prevented by antagonists of noradrenaline or CRF receptors. This is consistent with previous results showing that icv administration of orexin A strongly activates CRF-expressing neurons in the periventricular hypothalamic nucleus (PVN) and the central nucleus of the amygdala (CeA) [28]. In this same report, icv administration of orexin A also elevated intracranial self-stimulation (ICSS) thresholds, an effect similar to that seen with central administration of CRF [31]. These results indicate that the effects of icv orexin A on reinstatement might be caused by orexin-induced activation of CRF neurons. Additionally, a selective orexin A receptor antagonist blocked reinstatement of cocaine seeking induced by footshock stress [30], a behavioral paradigm known to depend on release of both noradrenaline and CRF [27,32,33]. Recent evidence already reviewed here indicates that this orexin–stress link involves orexin neurons in PFA–DMH, but not in the LH.

In addition to this influence of orexin on CRF neurons, recent anatomical results reveal projections from CRF neurons to orexinergic neurons [29]. CRF excites orexin neurons via the CRF-R1 receptor, and such activation is thought to maintain arousal during stressful events. For example, activation of PFA orexin neurons by footshock stress is severely compromised in mice whose CRF-R1 receptor has been knocked out, indicating that such activation might be mediated by CRF [29]. These data indicate not only that orexin can stimulate CRF neurons in the PVN and CeA, but also that CRF neurons in the PVN and CeA project back to orexin neurons causing further activation of the orexin system. Orexin neurons can also indirectly stimulate CRF neurons in the PVN through connections to neuropeptide-Y-containing neurons in the arcuate nucleus that in turn activate CRF-containing neurons in the PVN [34,35]. On the whole, these data indicate that PFA orexin neurons, as opposed to LH orexin neurons, respond to stressful events and might be activated by, and activate, CRF systems.

### Role of orexins in feeding and reward

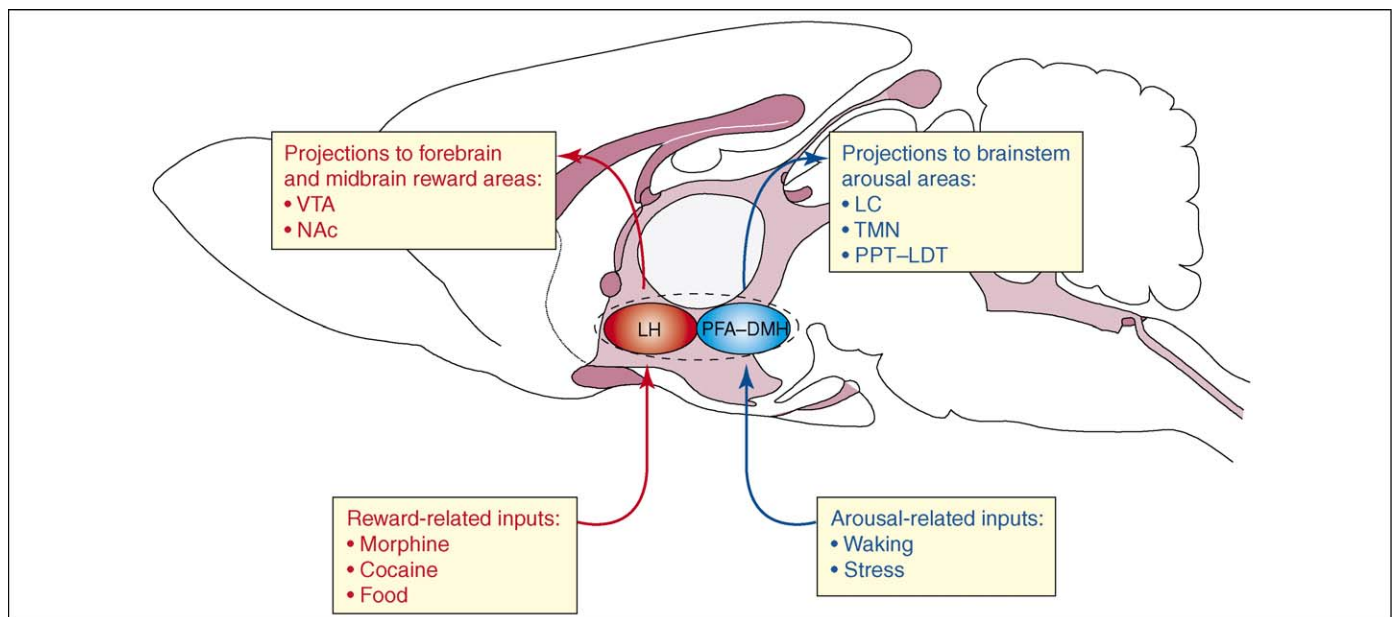
Anatomically, orexin neurons are in a good position to alter reward functioning. For instance, they heavily innervate both the dopamine-rich VTA and the nucleus accumbens (NAc) [36], structures that drive behaviors motivated by

either food or drug rewards. Moreover, orexin receptors are expressed at high levels in both of these areas [37–39]. Anatomical studies have further revealed that the shell region of the NAc might be more important for orexin-mediated behaviors than the core because the shell receives the majority of orexin inputs [8], it is the only region of the NAc to express orexin receptors [37,38], and it sends projections back to orexin neurons, the majority of which go to the LH region [40]. In light of this, orexin-expressing LH neurons, neurons in the NAc shell, and dopaminergic neurons in the VTA form a circuit that could be particularly important in reward processes.

Eating behavior depends on the connection between the LH and NAc [41,42]. For example, recent results showed that infusions of orexin A into the NAc shell augment feeding behavior [43]. In addition, infusions of the GABA<sub>A</sub> receptor agonist muscimol into the NAc shell strongly induced feeding behavior and simultaneously increased Fos expression specifically in orexin neurons in the LH [44]. By contrast, orexin neurons in the PFA did not show activation in response to intra-NAc infusions of muscimol but were stimulated by exposure to a novel environment, a situation evoking high arousal that did not activate the LH orexin neurons [44]. Harris *et al.* also found that environmental cues associated with novelty reward do not activate LH orexin neurons [11]. This reveals that not all reward cues activate LH orexin neurons. These data indicate that the NAc shell and orexin neurons in the LH are involved in circuits that regulate feeding, and support the view that LH orexin neurons function specifically in reward processes, whereas PFA orexin neurons are involved in arousal and stress responses.

Food deprivation has interesting effects that relate to both the orexin system and drug-seeking behaviors. For instance, 24 h of food deprivation is reported to increase the number of cells that express orexin in the hypothalamus, and to promote the formation of excitatory synapses and synaptic currents in orexin cells; these effects are reversed by re-feeding and blocked by leptin administration [45]. This same food restriction treatment also increases the reinforcing effects of both opiates and psychostimulants, lowers the threshold of ICSS reward, and reinstates drug-seeking behavior [46]. Adrenalectomy blocks the effect of acute food deprivation on reinstatement of cocaine seeking [47], suggesting that this might be an effect of stress. However, the increased rewarding effects of drugs, or the lowered ICSS thresholds, following food restriction might not be due to stress because they are not reversed either by adrenalectomy or by blocking corticosterone activity [46]. Furthermore, the lowering of ICSS thresholds by food deprivation is not consistent with stress-related CRF release because CRF administration raises ICSS thresholds [31]. Because the rewarding properties of both food and drugs of abuse might function through common brain substrates [46,48], it would not be surprising if LH orexin neurons mediate some of the effects of food deprivation to enhance reward mechanisms.

As already mentioned, the VTA contains high levels of orexin receptors and is heavily innervated by orexin neurons [36], and it participates in the control of behaviors related to both natural and drug reinforcers [49,50]. Orexin



**Figure 2.** Schematic of a sagittal section through the rat brain illustrating that orexin/hypocretin neurons (indicated by the dashed oval) located in the lateral hypothalamus (LH) or in the perifornical or dorsomedial hypothalamus (PFA-DMH) have distinct functional attributes. LH (but not PFA-DMH) orexin neurons are activated by stimuli that predict drug or food reward but not by a stressor. By contrast, stress activates PFA-DMH but not LH orexin neurons. In addition, orexin neurons in PFA-DMH (but not those in LH) are activated in proportion to arousal levels. These results lead us to hypothesize that LH and PFA-DMH populations of orexin neurons receive different inputs, and have different outputs, that result in distinct behavioral functions. Additional abbreviations: LC, locus coeruleus (noradrenergic neurons); NAc, nucleus accumbens; PPT-LDT, pedunculopontine nucleus and lateral dorsal tegmental nucleus (cholinergic neurons); TMN, tuberomammillary nucleus (histaminergic neurons); VTA, ventral tegmental area. Based on a diagram from Ref. [60].

administration in the VTA uniformly excites all GABAergic cells in this area, and has a variety of effects on VTA dopaminergic cells [39]. A recent study in rats [51] reported that intra-VTA infusions of orexin A increased dialysate dopamine levels in the prefrontal cortex (PFC) but not in the core region of the NAc. By contrast, another recent study [52] reported that the same intra-VTA dose of orexin increased dopamine release in the NAc shell. Because the shell and core regions of the NAc display numerous examples of functional heterogeneity [53], these differences in results are not surprising. It is interesting to speculate that these differences in shell and core dopamine levels in response to orexin administration in the VTA could be part of an important feedback loop given, as already mentioned, that the shell but not the core of the NAc sends projections to LH orexin neurons [40]. It was also reported [51] that intra-VTA infusions of orexin A increased the time that rats spent awake and grooming, and that these behaviors correlated well with elevated dopamine release in the PFC. These observations indicate that orexin release in the VTA might influence arousal via modulation of cortical dopamine neurotransmission. However, it is also noteworthy that dopamine in the PFC is essential for various drug-abuse-related behaviors, including reinstatement of cocaine self-administration [54]. Therefore, this orexin-mediated release of dopamine in the PFC might also have a role in reward processes.

The aforementioned data indicate that orexin neurons in the PFA-DMH region function primarily in arousal and stress processes, whereas orexin neurons in the LH do not. Instead, LH orexin cells are activated by reward-associated stimuli, and drive reward-seeking behavior (such as reinstatement of extinguished place preference) when

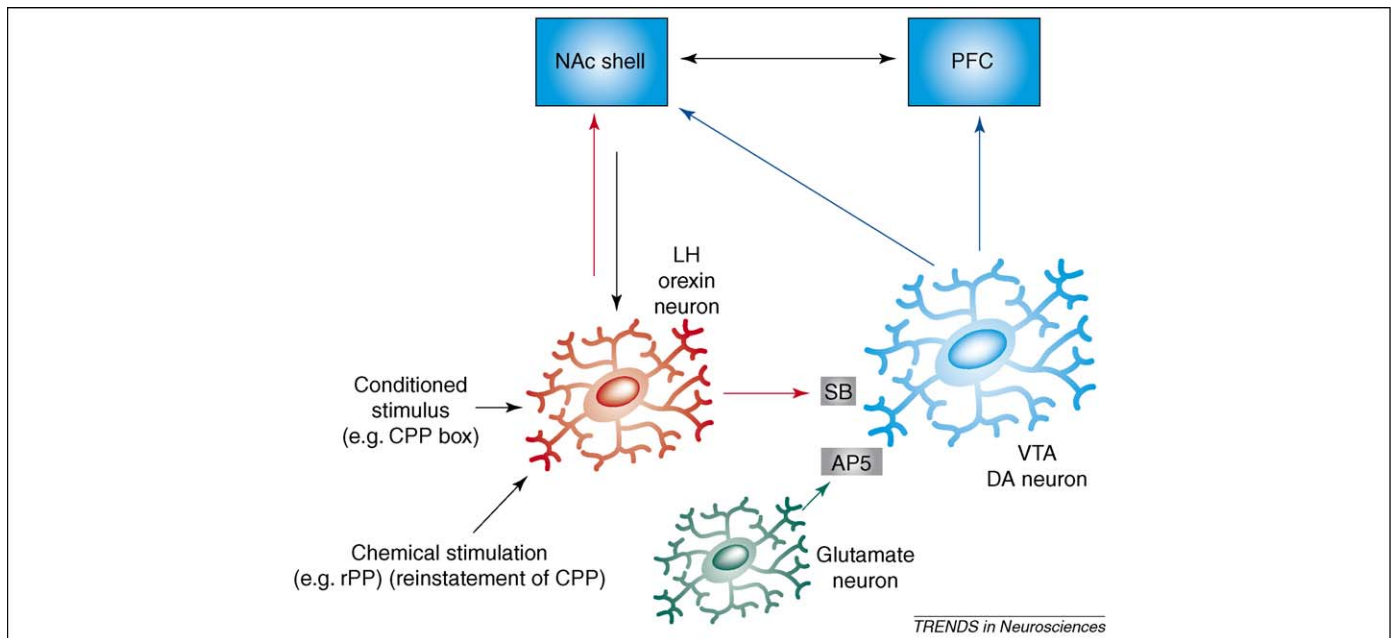
directly activated. These results lead us to propose that there is a functional dichotomy among populations of orexin neurons located in different subregions of the hypothalamus. The basis of this functional dichotomy might be differences in afferent and efferent projections to and from these subregions (Figure 2). Yoshida and colleagues [40] have recently provided support for this hypothesis. They reported that PFA-DMH orexin neurons are preferentially innervated by other hypothalamic regions involved in homeostatic and arousal-related drive states, whereas LH orexin neurons are preferentially targeted by brainstem areas involved in autonomic and visceral processing, and by reward-related areas such as the VTA and NAc shell. Unfortunately, at present there is little information about such possible distinctions in terms of efferent projections from hypothalamic orexin subregions.

These results indicate that orexin neurons in LH are preferentially involved in reward processing associated with specific types of reward (drugs and food, but not with novelty). In our lab, we have been particularly captivated by the reward-related functions of the LH orexin group. Several recent results lead us to propose that these cells are involved not only in reward processing, but also in reward-related learning and memory. The evidence for this viewpoint is presented next.

### Role of orexins in reward conditioning

As we have already described, stimulation of LH orexin neurons, or infusions of orexin A into the VTA, can reinstate an extinguished preference for a morphine-associated environment [11]. These reinstatement effects could result from production of a stress-like state or by reactivation of the original reward-learning circuitry. Data





**Figure 3.** Illustration of the proposed role of LH orexin neurons in a reward-based learning and memory circuit. During the acquisition of conditioned place preference (CPP) or cocaine sensitization, stimuli that are being conditioned (in association with primary rewards) activate LH orexin neurons, which release orexin in the VTA, enabling plasticity and conditioning to occur in dopaminergic (DA) neurons. This conditioning process can be blocked by microinjections into the VTA of either the orexin A antagonist SB334867 (SB) [52,55] or the NMDA receptor antagonist D(-)-2-amino-5-phosphonopentanoic acid (AP5) [57,58]. Dopaminergic projections from VTA to either the prefrontal cortex (PFC) or the nucleus accumbens (NAc) shell might provide the motivation for the reward-seeking behavior. The NAc shell is reciprocally connected with LH orexin neurons that might be important in the regulation of feeding [43,44]. Following learning, orexin release triggered by conditioned stimuli facilitates recall of the previously learned reward relationship [11], which might involve glutamate and plasticity in the VTA [57,58]. After extinction of reward-seeking behavior, activation of the LH orexin system [e.g. by microinjection of rat pancreatic polypeptide (rPP) into the LH, or of orexin A into the VTA] reinstates the reward-based memory and behavior (see main text) [11]. Red arrows indicate orexinergic projections, blue arrows indicate dopaminergic projections, green arrows indicate glutamatergic projections, and black arrows indicate projections where the neurotransmitter is not yet known.

we have reviewed here reveal that LH orexin neurons are not activated by stress, which leads us to favor the reactivation of the original circuitry. Results of several recent studies are consistent with this interpretation. Narita *et al.* [52] showed that infusions of an orexin A antagonist into the VTA prevented the acquisition of a conditioned place preference for morphine, indicating that orexin release in the VTA is necessary for learning the association between environmental cues and morphine reward. Furthermore, two studies have shown that orexins are involved in neuronal plasticity and the potentiation of synaptic transmission in the VTA [55] and hippocampus [56]. In the VTA [55], orexin A acutely potentiates responses of NMDA receptors, which in turn leads to late-phase AMPA-receptor-mediated plasticity in VTA dopaminergic neurons. Previously, blockade of either NMDA or AMPA glutamate receptors in the VTA was shown to prevent the acquisition of conditioned place preference for cocaine or morphine [57,58]. Borgland *et al.* also showed that administration of an orexin A antagonist blocks the plasticity that occurs in VTA dopaminergic neurons following cocaine administration [59], and the associated locomotor sensitization following repeated cocaine exposure. Together, these data (Figure 3) indicate that orexin release associated with exposure to drugs of abuse might alter synaptic plasticity within the VTA and consequently affect drug-stimulus conditioning.

Fadel and Deutch [36] revealed that the major source of orexin input to VTA is from LH orexin neurons, with fewer orexin afferents originating in the PFA or DMH. These results are consistent with those implicating LH orexin

neurons in reward processing, and with our view that these orexin cells are also involved in learning.

Other results indicate that LH orexin neurons are also involved in the memory for stimulus-reward relationships. This function is suggested by the aforementioned result that stimulation of LH, but not other, orexin neurons causes reinstatement of an extinguished place preference for morphine [11]. This might indicate that activation of these cells in an environment previously associated with morphine elicited a recall of the drug-environment relationship to produce reinstatement of preference. Moreover, the orexin antagonist SB 334867 attenuated the expression of a place preference for morphine after it had been learned [11]. Together, these results indicate that the projection of LH orexin neurons to the VTA functions not only in acute reward processing but also in reward-based learning and memory.

### Concluding remarks

The name orexin comes from the word orexigenic, which means to stimulate appetite. Mounting evidence indicates that the LH orexin system not only stimulates appetite for food, but also can stimulate an appetite for other rewards such as abused drugs. Activation of these neurons seems to be necessary for learning to associate drug rewards with specific environmental cues. This effect might be mediated through the generation of synaptic plasticity involving glutamate receptors in VTA. Furthermore, activation of this system can reinstate drug-seeking behaviors that have been extinguished, indicating a possible role for this system in memory for stimulus-drug associations and in drug

relapse. A parallel orexin system in the PFA–DMH is activated by arousing or stressful events and might help to maintain alertness. Activation of this system through stress also seems able to reinstate drug-seeking behaviors during abstinence. However, the mechanisms of relapse in the two cases seem to be different. We propose that the PFA–DMH orexin system drives relapse through activation of stress systems (perhaps involving CRF or noradrenaline), whereas the LH orexin system drives relapse through activation of brain circuits associated with reward learning. The orexin system, with its roles in both stress activation and reward-based learning and memory, could provide an important target for future pharmacotherapies designed to prevent drug relapse.

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