**Perspective**

**Drugs, sleep, and the addicted brain**

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The neurobiology of sleep and substance abuse interconnects, such that alterations in one process have consequences for the other. Acute exposure to drugs of abuse disrupts sleep by affecting sleep latency, duration, and quality [1]. With chronic administration, sleep disruption becomes more severe, and during abstinence, insomnia with a negative effect prevails, which drives drug craving and contributes to impulsivity and relapse. Sleep impairments associated with drug abuse also contribute to cognitive dysfunction in addicted individuals. Further, because sleep is important in memory consolidation and the process of extinction, sleep dysfunction might interfere with the learning of non-reinforced drug associations needed for recovery. Notably, current medication therapies for opioid, alcohol, or nicotine addiction do not reverse sleep dysfunctions, and this may be an obstacle to recovery [2, 3]. Whereas exposure to drugs of abuse is causal to sleep dysfunctions that further promote chronic use, sleep disorders in turn are risk factors for substance abuse and their severity can predict the prognosis of substance use disorders (SUD) [4]. Sleep disruption results in a cumulation of risk factors that drive drug abuse, including increasing the sensitivity to pain, acting as a stressor, and biasing toward a negative effect.

Recognizing and treating sleep disorders may be an important preventive measure against future drug misuse and SUD. Despite convergent evidence linking sleep and substance abuse, and the therapeutic potential that can emerge from elucidating the biology underlying this link, this has been a relatively neglected area of research. A first step in advancing this area is to identify how the circuits and substrates that regulate sleep and arousal intersect with those that mediate reward and also how they are targeted by drugs of abuse.

The locus coeruleus (LC)—norepinephrine (NE) system is a diffuse forebrain-projecting system that is involved in arousal and also is a primary target of drugs of abuse, including nicotine, stimulants, opioids, and cannabinoids. LC–NE neuronal activity is positively correlated to the state of arousal, and LC neurons are most active during waking and are off during REM sleep [5]. Selective LC activation is sufficient to elicit cortical arousal, and conversely, selective LC inhibition prevents cortical activation by stressors, indicating that this system is important in regulating cortical arousal in response to stressors and other salient stimuli [6, 7]. The stress-related neuropeptide, corticotropin-releasing factor (CRF), mediates stress-induced LC excitation, and endogenous opioids that innervate the LC exert an opposing effect that may serve to restrain excessive activation and promote recovery after stress termination [8]. Opioid tolerance would be expected to enhance stress-induced activation of this arousal system, and promote a cycle of drug seeking to tone down the excessive response. LC neurons are robustly activated during opioid withdrawal and this has implicated the LC–NE system in opioid-withdrawal signs, including the hyperarousal and insomnia associated with withdrawal [9]. Notably, α2-adrenergic antagonists (lofexidine and clonidine) that inhibit LC discharge are clinically used for the attenuation of opioid and alcohol withdrawal to reduce peripheral symptoms from sympathetic activation, such as tachycardia, as well as central symptoms, such as insomnia, anxiety, and restlessness. Their utility in suppressing symptoms during protracted abstinence, such as insomnia, along with its associated adverse consequences (irritability, fatigue, dysphoria, and cognitive impairments) remains unexplored.

Like LC–NE neurons, the raphe nuclei (including the dorsal raphe nucleus—DRN) serotonin (5-HT) neurons modulate sleep and wakefulness through widespread forebrain projections. The role of this system in sleep is complex. Raphe nucleus lesions trigger insomnia [10, 11], and during the awake state, the cumulative 5-HT, released from the raphe into the basal forebrain (including the nucleus basalis, which is the main cholinergic input to the cortex, and regulates arousal), is believed to serve as a sleep-promoting factor [11]. However, 5-HT neurons are active during waking, decrease their activity during slow-wave sleep, and cease firing during REM sleep, as is the case for LC–NE neurons [12, 13]. Notably, DRN-5-HT neurons are implicated in the arousal from sleep in response to hypercapnia [14], which is impaired during opioid-induced overdoses, and further work is required to assess how to target the serotonin system as a way to prevent opioid-induced overdoses or to improve outcomes when naloxone cannot completely reverse them (Table 1).

Like the LC–NE and DRN-5-HT systems, the histamine (HA) neurons of the tuberomammillary nucleus form another diffusely projecting arousal system that is active during waking only and these neurons are activated by opioids, which can further contribute to sleep disruption associated with chronic opioid use. HA promotes arousal through activation of cortical and basal forebrain neurons, effects that are primarily mediated by H1 receptors [15, 16]. Thus, the H1 receptor may be an alternate target for treating sleep dysfunction associated with abstinence.

In contrast to the LC–NE and DRN-5-HT systems, midbrain dopamine (DA) neurons were not considered to be sleep-related, because they show little change in discharge rate during the sleep/wake cycle other than bursting during paradoxical sleep. However, the wake-promoting actions of drugs that enhance DA signaling are widely recognized and used for clinical purposes [17, 18]. Transgenic modifications that enhance DA neurotransmission in mice, such as deletion of the DA transporter gene, result in increased wakefulness [19], whereas deletion of DA D2 receptors (D2R) decreases wakefulness [20]. Further, recent optogenetic studies demonstrated that activation of DA neurons in the ventral tegmental area (VTA) but not substantia nigra increases wakefulness [21]. These arousal effects are mediated by.
VTA projections to the nucleus accumbens, because optogenetic activation of DA terminals here, but not in other terminal regions, also promoted wakefulness. Therefore, this specific DA circuit is a node that regulates the rewarding effects of drugs of abuse and one that mediates arousal, including that elicited by salient and rewarding stimuli.

The endogenous cannabinoid system (ECS) that signals through cannabinoid CB1 and CB2 receptors, which are targets of marijuana, is also involved in circadian rhythm and the regulation of the sleep–wake cycle [22, 23]. Acutely, cannabis is sleep-promoting and decreases latency, increases sleep time, increases slow-wave sleep, and decreases REMs [1, 23]. Consistent with this, CB1 antagonists increase wakefulness and decrease slow-wave sleep and REMs and conversely, the endogenous CB1 agonist, anandamide enhances slow-wave sleep and REM [24]. The effects of CB1 signaling may be mediated through the sleep-promoting molecule, adenosine because doses of anandamide that promote sleep increase adenosine release in the basal forebrain [25]. Notably, adenosine is the target of caffeine, which is an adenosine receptor antagonist that is widely used to increase arousal. Another potential mechanism for the sleep-promoting effects of endocannabinoids is through their opposing regulation of neuronal activity in the lateral hypothalamus, inhibiting the activity of arousal-promoting orexin neurons (see below), while increasing the activity of sleep-promoting melanin concentrating hormone neurons [26].

With chronic use, tolerance occurs to the sleep-enhancing effects of cannabis, and abstinence is characterized by unusual dreams and poor sleep quality that is predictive of relapse [27]. ECS disruption with chronic marijuana use is likely to underlie the long-lasting insomnia commonly observed during abstinence in cannabis abusers.

The orexin system that derives from the posterior lateral hypothalamus is like the LC–NE, DRN–5-HT, and TMN–HA systems in that the cells only fire during waking and are silent during sleep phases [28]. It is unique in being essential for sustaining the waking state, as its disruption in patients with narcolepsy leads to periodic and abrupt interruptions of the conscious state. The cluster of orexin neurons in the hypothalamus is a node that links to the other arousal-related nuclei, including basal forebrain cholinergic neurons, TMN–HA neurons, DRN–5-HT neurons, VTA–DA neurons, lateral dorsal tegmental cholinergic neurons, and LC–NE neurons (Fig. 1). It is poised to orchestrate a synchronous activation of multiple arousal systems. In addition to its role in arousal, orexin has a role in the rewarding effects of drugs of abuse, including those of opioids [29]. For example, narcoleptics that have low orexin levels do not abuse opioids and mice with genetic deletion of orexin show decreased opioid-addiction potential, implicating orexin in the initial rewarding effects of opioids [29]. Orexin neurons are activated by reward and project to the DA neurons in VTA that innervate the nucleus accumbens and mediate reward, which they also influence via their direct projections to it. Chronic opioid exposure upregulates orexin in humans and rodents [30]. Postmortem brains of heroin users showed increases in orexin neuron numbers in the lateral hypothalamus and reverse translation studies verified that chronic opioid administration in rodents also increased the number of orexin neurons in their lateral hypothalamus. The upregulation of orexin would be expected to create a state of hyperarousal and may underlie the insomnia observed both in treated and non-treated opioid users. Preclinical studies, demonstrating that orexin microinjection into the VTA increases cocaine self-administration and reinstates cocaine-conditioned place preference, also implicated orexin in cocaine’s rewarding effects. It has been suggested

| Neurotransmitter | Drug            | Intoxication | Abstinence        |
|------------------|----------------|--------------|------------------|
| NE               | Stimulants     | Enhanced     | Reduced during early stages of withdrawal |
| Arousing         | Opioids        | Reduced      | Hyperexcitable   |
|                  | Alcohol        | Reduced      | Hyperexcitable   |
| S-HT             | Stimulants     | Enhanced     | Reduced          |
| Arousing/sedating| Ecstasy        | Enhanced     |                  |
|                  | Nicotine       | Enhanced     |                  |
| DA               | Stimulants     | All drugs    | D2R, DAT, and DA release are downregulated |
|                  | Opioids        | enhance DA   |                  |
|                  | Nicotine       |              |                  |
| Histamine        | Opioids        | Enhanced     | Tolerance        |
| Arousing         | Alcohol        | Reduced      |                  |
| Nicotine         | Nicotine       | Enhanced     | Tolerance        |
| Arousing         | Alcohol        | Reduced      |                  |
| Orexin           | Cocaine        | Enhanced     | Upreregulated    |
| Arousing         | Opioids        | Enhanced     | Upreregulated    |
| Mu opioids       | Nicotine       | Enhanced     | Tolerance of MOR |
| Sedating         | Alcohol        | Enhanced     |                  |
| Adenosine        | Caffeine       | Reduced      | Tolerance        |
| Sedating         |                |              |                  |
| Cannabinoids     | Cannabis       | Enhanced     | Downregulation   |
| Sedating         |                |              |                  |

Because the effects of a neurotransmitter on arousal and sleep may differ depending on the brain region it targets, in some instances, the effects are mixed as is the case for serotonin. Also, the effects can differ during early versus protracted withdrawal, such as is the case for cocaine that leads to enhanced sedation that can last up to 3–4 weeks post withdrawal to then be followed by protracted insomnia.

Fig. 1 Schematic depicting efferent projections of lateral hypothalamic orexin neurons. The orexin system is positioned to influence cognitive function, arousal, and rewarding. Orexin neurons have broad forebrain projections. Cortical projections may modulate cognitive aspects of substance use behavior such as decision-making. In addition, they project to arousal-related nuclei, including the locus coeruleus (LC), which expresses norepinephrine (NE), dorsal raphe nucleus (DRN), which expresses serotonin (5-HT), lateral dorso-temoral nucleus (LDT), which expresses acetylcholine (ACH), tuberomammillary nucleus (TMN), which expresses histamine (HA), and nucleus basalis of Meynert (NBM), which expresses ACH. These nuclei in turn have diffuse projections throughout the forebrain. Orexin neuronal projections to the ventral tegmental area (VTA) and nucleus accumbens (NAc) are poised to modulate reward and to make rewarding stimuli arousing.
that orexin is specifically engaged in substance abuse during elevated motivational states, such as when the effort to obtain the drug is high [29] or when animals are stressed [31]. For example, orexin antagonists only affect self-administration under conditions that require a relatively high effort, such as progressive ratio schedules, or when drug seeking is triggered by cues or stress, suggesting that it may be particularly active during relapse. This would be consistent with a state of heightened arousal that accompanies craving. These findings provide a rationale for the evaluation of orexin antagonists, such as suvorexant, a drug currently approved for use for insomnia, as therapy for substance use disorders and for the development of new ones. These agents may provide a two-fold benefit by preventing two distinct but interrelated effects of orexin, potentiation of reward and arousal effects, which could help attenuate drug reward and improve sleep disturbances.

Although it is becoming well accepted that there are neurobiological links between sleep dysfunction and substance abuse behavior that result in comorbidity, research is still in its infancy. Earlier, we discussed a simplified anatomical framework that identifies some of the relevant links for this comorbidity, but there are likely other pathways and substrates, some of which still need to be discovered. The precise functional interactions between these different regions and their involvement in the trajectory of drug use has not been explored in any depth. Likewise, how the interaction between sleep and substance use is shaped by genetics, life events, sex, and circadian rhythms remains unknown. Further research to fill the knowledge gaps at the intersection of sleep, drug reward, and addiction will help identify treatment targets that improve the quality of life of individuals suffering from sleep and substance use disorders.

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