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Sleep loss and addiction

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ABSTRACT

Reducing sleep hours is a risk factor for developing cardiovascular, metabolic, and psychiatric disorders. Furthermore, previous studies have shown that reduction in sleep time is a factor that favors relapse in addicted patients. Additionally, animal models have demonstrated that both sleep restriction and sleep deprivation increase the preference for alcohol, methylphenidate, and the self-administration of cocaine. Therefore, the present review discusses current knowledge about the influence of sleep hours reduction on addictivebehaviors; likewise, we discuss the neuronal basis underlying the sleep reduction-addiction relationship, like the role of the orexin and dopaminergic system and neuronal plasticity (i.e., delta FosB expression). Potentially, chronic sleep restriction could increase brain vulnerability and promote addictive behavior.

1. Introduction

It is well established that sleep loss results in significant negative consequences, such as cognitive performance impairment, deterioration of the immune response to infection, imbalances in hormone secretion, and metabolic alterations (Dijk and Landolt, 2019). Additionally, sleep loss facilitates drug-taking behaviors in humans and drug-seeking in rats that have been previously trained in drug self-administration (Puhl et al., 2013; Roehrs et al., 1999).

Clinical studies have suggested that low sleep quality is a factor that predicts relapse in addicts (Brower, 2001; Clark et al., 1998; Foster and Peters, 1999; Gillin et al., 1994), proposing a relationship between sleep disruption and substance abuse. In addition, some authors have reported that insomnia could predict the development of alcohol abuse (He et al., 2019; Weissman et al., 1997). Given that insomnia is a condition of chronic insufficient sleep, it is plausible to suggest that a gradual decline in sleep time can be a factor that elicits drug consumption. Currently, there are excellent reviews on the topic (Ahrens and Ahmed, 2020; Fragale et al., 2021; McGregor et al., 2021). However, the question remains unresolved about how sleep loss affects the brain to induce drug preference or drug addiction. Potentially, the brain reward circuity is a target affected by sleep deprivation. In the present review, we discuss some evidence supporting how reducing sleep time favors drug consumption. Furthermore, we propose a hypothetical model of interaction between sleep loss and drug use.

2. The brain circuit of the reward

The concept of addiction has evolved over time, from a lack of will in addicts to a brain disorder (Heather, 1998). Today, mental health professionals consider addiction a neuropsychiatric disease characterized by a recurring desire to continue taking drugs despite the knowledge of

Abbreviations: (p)CREB, (phosphorylated) cAMP response element-binding protein; AMPAR, AMPA glutamate receptor; BDNF, brain-derived neurotrophic factor; DA, dopamine; DR, dorsal raphe nucleus; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; GABA, gamma amino butyric acid; ICD-10, Tenth Revision of the International Classification of Diseases; ICSS, intracranial self-stimulation; IEGs, immediate early genes; LC, locus coeruleus; LHA, lateral hypothalamic area; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; NREM, non-rapid eye movement; ORX, orexin; PFC, prefrontal cortex; REM, rapid eye movement; TMN, tuberomammillary nucleus; vACC, ventral anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area.

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their harmful consequences (Goldstein and Volkow, 2002). The most used diagnostic criteria for drug addiction is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and the Tenth Revision of the International Classification of Diseases and Related Health Problems (ICD-10), which evaluate cognitive, physiological, and pathological behavioral patterns related to the use of the substance such as time spent, tolerance, withdrawal, and control lost among other features of addiction to diagnose and evaluate the progress of treatments (American Psychiatric Association, 2013). Additionally, the development of new technologies and products has a significant impact on mental health, as it has been discovered that behavioral and physiological patterns of addiction are developed with the use of the Internet (Mihajlov and Vejmelka, 2017), the consumption of refined sugar (Jacques et al., 2019; Westwater et al., 2016), among other food, which led to the establishment of the term behavioral addictions that comprises gambling, food addiction, internet addiction and mobile phone addiction(Zou et al., 2017).

The biological basis of addiction is a complex and heterogeneous phenomenon since the main pharmacological effects of some drugs of abuse are sedatives (i.e., ethanol, barbiturates, opiates, and benzodiazepines), while other drugs act as CNS stimulants (i.e., nicotine, cocaine, amphetamines), meaning they have opposite pharmacological effects. There are also substances with anti-nociceptive effects capable of inducing addiction, such as cannabinoids and opiates. These different mechanisms underlie differences in the symptoms of addiction, i.e., opiates are characterized by strong physical withdrawal symptoms, whereas cocaine withdrawal only occurs in a subset of users and symptoms are subtler than those produced by drugs such as opiates (Sofuoglu et al., 2003). The inclusion of behavioral addictions mentioned above adds even more differences between the substances and stimuli that can induce dependence. Nevertheless, despite the tremendous pharmacological disparities, addictive substances and stimuli share some common features in their development and neurobiological roots.

Generally, the first stage of drug consumption is an instrumental response driven by the rewarding effects of the drugs, followed by their chronic use that leads to plastic changes that range from a molecular and cellular level to neuronal networks in several brain regions that regulate drug use. Then, drug consumption becomes a conditioned behavior that consumers can no longer control, characterized by specific phases that repeat in a cycle over and over: bingeing, withdrawal, and craving. Every stage is characterized by functional and anatomical disruptions in different brain regions, among which dopaminergic areas, the prefrontal cortex (PFC), amygdala, and lateral hypothalamus are extensively involved.

Activation of the dopaminergic system is crucial for establishing the psychotropic effects of drug intake since practically all addictive drugs act as dopamine agonists in specific areas such as the ventral tegmental area (VTA), substantia nigra, dorsal striatum, and the nucleus accumbens (NAc) located in the ventral striatum; all these regions have been involved in reward, conditioning, and habit formation, and are known as the core reward circuitry (Gardner, 2011). Consequently, the involvement of these areas in addiction has been extensively explored. The VTA is a central hub of reward and motivation located near the base of the midbrain with dopamine, glutamate, and GABA neurons that target the medial prefrontal cortex (mPFC) and the shell part of the NAc, but also receives inputs from the lateral hypothalamic area (LHA) (Peyron et al., 1998). The NAc is connected to limbic structures such as the amygdala, hippocampus, and PFC. Both main parts of the NAc (Shell and core) regulate reward and drug-seeking behavior through different inputs (di Chiara et al., 2004; Kalivas and Volkow, 2005; Sellings and Clarke, 2003).

The PFC controls executive functions and motivation, regulating behavioral inhibition, attention, cognitive control, and decision making. Specifically, the ventromedial prefrontal cortex (vmPFC) is involved in decision-making and suppression of inappropriate behaviors and seems to be mainly engaged in the capacity of the individual to seek or inhibit drug use such as alcohol, nicotine, heroin, or cocaine (Moorman et al., 2015; Muller Ewald and LaLumiere, 2018). (Goldstein and Volkow, 2002) reviewed the participation of the heterogeneous functions of the PFC that can be affected by drug addiction, among which are the orbitofrontal cortex, anterior cingulate cortex, and dorsolateral prefrontal cortex, mPFC, and vmPFC before mentioned.

The amygdala processes emotional and behavioral responses such as fear, aggression, and anxiety-related stimuli through connections to areas such as the PFC, NAc, and hindbrain (Sharp, 2019). Specifically, stress-induced changes in the activity of the basolateral nucleus of the amygdala increase the activity of efferent neurons to the NAc core, which enhances motivation for appetitive reward, triggering abnormal motivated behavior such as drug addiction (Sharp, 2019). Those findings support the widely observed relation between the effects of stress responses on the amygdala and the increase in cue reactivity and drug self-administration responsible for relapse to drug-taking behavior.

3. Sleep deprivation, sleep restriction, and substance use disorder

Behaviorally, sleep can be characterized by stereotypical behaviors like prolonged behavioral quiescence, a species-specific posture, increased arousal threshold to respond to external stimuli, and homeostatic rebound following sleep deprivation (Datta, 2010; Keene and Duboue, 2018; Markov et al., 2012). Furthermore, sleep in mammals (including humans) can be divided into two stages based on brain wave activity measured by electroencephalographic recordings (EEG): the non-rapid eye movement (NREM) sleep and the rapid eye movement (REM) sleep (Markov et al., 2012; Swick, 2012); this later phase is related to a more frequent content of emotional and perceptually vivid dreams in humans (Scarpelli et al., 2019).

Additionally, sleep is regulated by two basic processes: a homeostatic process and a circadian process (Borbély et al., 2016; Deboer, 2018). The homeostatic factor represents sleep debt, observed by an increase in the need for sleep (sleep pressure) as duration of prior wakefulness increases. Normally, sleep propensity increases during waking hours reaching its peak at sleep time and declines during sleep, with the lowest point on awakening in the morning. When sleep is lost the homeostatic drive is increased, and this loss is compensated by extending subsequent sleep and/or deepening subsequent sleep (reflected as increased EEG slow wave activity) (Deboer, 2018, 2013; Porkka-Heiskanen, 2013). On the other hand, the circadian control of sleep refers to the oscillation of 24-h cycles of behavior, entrained to day and night, driven by an endogenous circadian peacemaker (or biological clock) rooted in the suprachiasmatic nucleus (SCN) of the hypothalamus; the entrainment of involves SCN processing of photic information via the retina, then a synchronization of its own neuronal cellular clocks by activation of intracellular transduction pathways leading to the phase-locking of clock gene expression, and finally the transduction of the “internal day” to a network of peripheral clocks (Deboer, 2018; Golombek et al., 2013; Roenneberg and Merrow, 2016). These two mechanisms appear to exert mutual influence on each other, as well as additive effects, by regulating the timing, depth, and maintenance of sleep. In this sense, Deboer (2018) states that under normal conditions a strong rhythm will benefit sleep, and good healthy sleep will strengthen clock functioning; however, when the relationship between sleep homeostatic mechanisms and the circadian control is disturbed, it could strengthen in a vicious circle and disturbed sleep may result in a less functional circadian clock, which in turn reduces the quality of sleep.

If the correlation between behavioral sleep-like states and the electrophysiological recordings are considered, sleep seems ubiquitous throughout the animal kingdom (Keene and Duboue, 2018). Moreover, the conservation across diverse animal species suggests that sleep fulfills a common purpose that benefits animal survival (Miyazaki et al., 2017). In contrast, poor sleep quality has detrimental effects on health, body

functions, and behavior (Itani et al., 2017; Krause et al., 2017; Krueger et al., 2016; Zhu et al., 2019). Recently, numerous studies have reported a decline in sleep duration and an increase in poor sleep quality in modern societies (Chaput et al., 2017; Sheehan et al., 2019; Varghese et al., 2020), especially among adolescents (Karan et al., 2021; Otsuka et al., 2021; Sousa-Sá et al., 2021).

Insufficient sleep has become a concern in many countries, given its association with detrimental health outcomes, including obesity, diabetes type 2, hypertension, cardiovascular disease, and cognitive and emotional processes (Chaput et al., 2018; Frenda and Fenn, 2016; Owens et al., 2014). Additionally, a vast literature has reported the influence of poor sleep quality on substance use disorders. For instance, a 1-year follow-up epidemiologic survey - over 10,000 adults participated - reported that individuals who suffered insomnia were at higher risk (odds ratio of 2.3) of developing alcohol abuse (Weissman et al., 1997). In another study, insomnia appeared as a robust predictor of relapse in alcoholic patients receiving treatment for their alcohol dependence (Brower, 2003). Additionally, a group of alcoholic patients in recovery showed that 52% of the participants experienced sleep problems before reaching alcohol dependence (Currie et al., 2003).

Table 1
Effects of sleep loss on reward processing in animal models.

Reward	Model	Intervention	Result	Authors
Intracranial brain self-stimulation (ICSS)	Adult male Holtzman rats	REM sleep deprivation for 23 h/4 d	↓ ICSS thresholds of current intensity ↑ Rates of responding	(Steiner and Ellman, 1972)
Carbohydrate rich diet	Male albino rats	REM sleep deprivation for 72 h	↑ Intake	(Bhanot et al., 1989)
Food, and sucrose pellets	Adult Sprague-Dawley	REM sleep deprivation for 5 d	– Food intake ↓ Rate of responding in acquisition ↓ Maintenance of operant task	(Hanlon et al., 2005)
Sucrose pellets (20 mg)	Male C57BL/6 mice	Total sleep deprivation for 6 h	↑ Self-administration	(Liu et al., 2016)
Palatable food	Male C57BL/6 mice	REM sleep deprivation for 12 h	↑ Intake	(McEown et al., 2016)
Alcohol (10% v/v)	Adult male Long-Evans rats	REM sleep deprivation for 7 d	↑ Intake	(Aalto and Kiianmaa, 1984a)
Alcohol (10% v/v)	Adult male Long-Evans rats	REM sleep deprivation for 4 d	↑ Intake	(Aalto and Kiianmaa, 1984b)
Alcohol (10% v/v)	Adult male Long-Evans rats	REM sleep deprivation for 6 d	↑ Intake with ad libitum access	(Aalto and Kiianmaa, 1986)
Alcohol (1.8 or 2.2 g/kg)	3-month-old Swiss EPM-M1 female and male mice	REM sleep deprivation for 48 h	↓ Locomotor activity	(Araujo et al., 2006)
Alcohol (10% v/v)	Male and female Fisher and Lewis rats	Phase advances every 3 weeks	↓ Intake	(Rosenwasser et al., 2010)
Alcohol (2 g/kg)	Adult male C57BL/6 mice	Sleep restriction for 3 d	↓ Sensitivity to motor- impairing effects	(Clasadonte et al., 2014)
Alcohol (10% v/v)	Male Wistar rats	Forced activity during resting phase and constant light	↑ Intake	(Reséndiz-Flores and Escobar, 2019)
Alcohol (15% v/v)	Male Wistar rats	Total sleep deprivation for 4 h/7 d	↑ Intake	(García-García et al., 2021)
Morphine (5 mg/kg)	Male Sprague-Dawley rats	Total sleep deprivation for 6 h	– Reward memory retrieval ↓ Memory reconsolidation ↓ Priming of reward memory	(Shi et al., 2011)
Amphetamine (2.0 mg/kg)	3-month-old male C57BL/6 J mice	REM sleep deprivation for 48 h	↑ Hyperlocomotion ↑ Behavioral sensitization – Association with contextual cues	(Frussa-Filho et al., 2004)
Amphetamine (2.0 mg/kg)	3-month-old male C57BL/6 J mice	Total sleep deprivation for 6 h	↑ Hyperlocomotion ↑ Behavioral sensitization	(Saito et al., 2014)
Amphetamine (2.0 mg/kg)	Adult and adolescent male Swiss EPM-M1 mice	REM sleep deprivation for 48 h	↑ Behavioral sensitization	(Kameda et al., 2014)
Amphetamine (2.0 mg/kg)	3-month-old male C57BL/6 J mice	REM sleep deprivation for 6 h	– Hyperlocomotion – Behavioral sensitization	(Saito et al., 2014)
Amphetamine (2 mg/kg)	3-month-old male Wistar rats	Total sleep deprivation for 6 h/2 d	↑ Conditioned place preference	(Berro et al., 2018)
Methamphetamine (0.01% m/v)	3-month-old male Sprague-Dawley rats	4 phase shifts in 2 weeks	↑ Intake	(Doyle et al., 2015)
Methamphetamine (0.25 mg/kg)	Adult male Wistar rats	REM sleep deprivation for 24 h	↑ Reinstatement of condition place preference	(Karimi-Haghighi and Haghparast, 2018)
Methamphetamine (2 mg/kg)	Male Wistar rats	REM sleep deprivation for 48 h	↓ Reward memory retrieval – Memory reconsolidation ↑ Memory reactivation ↑ Hyperlocomotion – Intake	(Shahveisi et al., 2019)
Morphine (0.5 mg/mL in 0.02% saccharin)	Adult male C57BL/6NTac	Total sleep deprivation for 8 h/ 3 d by week	↓ Preference – Conditioned place preference	(Eacret et al., 2022)
Cocaine hydrochloride (7 mg/kg)	Adult male Wistar rats	REM sleep deprivation for 96 h	↑ Stereotypy behavior ↑ Exploratory activity	(Andersen et al., 2005)
Cocaine hydrochloride (0.33 mg/infusion)	3-month-old male Wistar rats	Total sleep deprivation for 4, and 8 h	↑ Rate of self-administration	(Puhl et al., 2009)
Cocaine hydrochloride (0.33 mg/infusion)	3-month-old male Sprague-Dawley rats	Chronic sleep restriction in a two 4-days cycles	↑ Goal-directed responding ↑ Self-administration	(Puhl et al., 2013)
Cocaine (15 mg/kg)	3-month-old Swiss male mice	Total sleep deprivation for 6 h	↓ Extinction of association with contextual cues	(Berro et al., 2014a)
Cocaine (15 mg/kg)	Three-month-old Swiss male mice	Total sleep deprivation for 6 h	↑ Hyperlocomotion	(Berro et al., 2014b)
Cocaine (0.003–0.3 mg/kg)	Adult male rhesus monkeys	One night of sleep disruption	– Self-administration	(Brutcher and Nader, 2013)
Cocaine (15 mg/kg)	Adult male C57BL/6 mice	Total sleep deprivation for 4 h/5 d	↓ Behavioral sensitization at initial administration ↑ From second administration	(Bjorness and Greene, 2018)
Cocaine (3, 8 mg/kg)	Adult male C57BL/6 mice	Total sleep deprivation for 4 h	↑ Conditioned place preference	(Bjorness and Greene, 2020)

* ↑ increase response; ↓ decreased response; – no significant difference related to control groups.

Although most of the studies on sleep have focused on the relationship between sleep and alcohol abuse, evidence demonstrates that poor sleep quality increases the rates of relapse among other drug users. For instance, a one-week follow-up study showed that participants who reported poor sleep quality (Pittsburg Sleep Quality Index) before quitting cannabis had a greater risk factor for relapse (Babson et al., 2013). Similarly, data analysis from the Drug Abuse Treatment Outcome Studies conducted from 1991 to 1994 demonstrated that a lifetime history of insomnia and hypersomnia was associated with a higher frequency of cocaine and heroin use (Dolsen and Harvey, 2017).

Furthermore, it has been shown that poor sleep quality could be a risk factor for increasing drug consumption. For example, a prospective 5-year cohort follow-up study showed that transitioning from adequate to inadequate sleep duration enhances daily cigarette consumption, brings forward the time of the first cigarette, increases the difficulty in not smoking for a day, and influences a higher nicotine addiction (Patterson et al., 2018). Moreover, a protocol of 4 days of sleep restriction in healthy volunteers demonstrated that reduced sleep time enhances the preference for methylphenidate (Roehrs et al., 1999).

This evidence suggests a possible bi-directional relationship between sleep disruptions and substance abuse, meaning that sleep loss may contribute to the process of addiction and that it is not just a consequence of the illness. However, considering that addiction is a three-stage cycle (binge/intoxication, withdrawal/negative affect, and craving) (Koob and Volkow, 2016), human studies become somehow difficult because of: 1) sleep alterations are not always present in drug users; 2) drug users that meet the criteria of dependence often have taken drugs over the course of several years, varying the amounts of drug used, and often using multiple drugs purposefully (i.e., cocaine, nicotine, and alcohol at the same time) or inadvertently (i.e., fentanyl added to cocaine), and; 3), the recruitment of non-drug users to test the effects of these substances on sleep would be unethical for the amount of drug needed to study bingeing/withdrawal/craving situations. Thus, animal models become relevant to investigate how sleep loss influences the response to drugs and natural rewards in every stage of addiction (Table 1).

In general, sleep function has been hypothesized to be involved in memory consolidation, clearance of brain metabolites, brain development, neuronal plasticity, spine formation, immune function, caloric use, and brain energy stores (Krueger et al., 2016; Miyazaki et al., 2017). Nevertheless, distinct functions have been attributed to NREM and REM sleep. For instance, NREM has been associated with the secretion of growth hormone (Hollf et al., 1991; Honda et al., 1969), synaptic plasticity, and memory consolidation (Chauvette et al., 2012; Tononi and Cirelli, 2014), whereas REM sleep has been associated with memory consolidation to a greater extend (Xia and Storm, 2017). Thus, the distinction between total sleep deprivation, chronic sleep restriction, and sleep disruption/fragmentation protocols and their influence on every stage of the process of addiction must be considered.

On the one hand, sleep deprivation refers to sleep loss for a specific period extending the vigilance state (Bobić et al., 2016); and, considering the two sleep subdivisions, there can be three potential types of sleep deprivation: 1) total sleep deprivation, where the animal or subject is deprived of both NREM and REM; 2) NREM sleep deprivation, where the animal or subject is expected to be only deprived of this stage; and 3) REM sleep deprivation, which is referred to the selective shortening time spent in REM sleep, often taking advantage of the muscle atonia in rodent studies (Mallick and Singh, 2011). On the other hand, chronic sleep restriction implies a long-term shortening of the usual sleep duration physiologically expected for a given age, and sleep fragmentation refers to the frequent interruption of sleep by multiple arousals due to external disturbances (Bobić et al., 2016). Nevertheless, caution must be taken since none of these types of sleep deprivation are actually selective. For instance, as mammals typically enter REM sleep from a period of NREM sleep, total sleep deprivation and NREM sleep deprivation are practically the same; similarly, when REM sleep deprivation is carried out a significant NREM sleep loss is seen as well. Likewise, sleep architecture must be considered when sleep deprivation occurs in humans due to the slow-wave sleep predominance during the first third of the night, and the most extended REM periods found in the last third of the night; however, once again, sleep deprivation during the first half of the night does not translate into selective NREM sleep deprivation since REM sleep is still present and vice versa.

These protocols have detrimental effects on cognitive functions, mainly over sustained attention, vigilance, and working memory (Frenda and Fenn, 2016), but with slight differences. For example, one study reported that participants who underwent 4 or 6 h of sleep restriction for 14 days showed cognitive deficits in attention and working memory comparable to participants who endured one or two nights of total sleep deprivation, suggesting that the harmful effects of chronic sleep restriction accumulate over time, eventually matching the immediate effects of total sleep deprivation (van Dongen et al., 2003).

In this context, animal models have explored the effect of sleep loss in memory consolidation, the process of extinction in drug-environment conditioning, and the associative memory between contextual cues and rewarding effects of drugs; many of these studies have obtained different results. For example, total sleep deprivation for 6 h during the rest phase, just before behavioral evaluations, showed detrimental effects on the extinction of drug-environment conditioning in cocaine sensitized mice (Berro et al., 2014a). Contrary, a 48 h REM sleep deprivation episode only impaired drug reward memory when sleep deprivation occurred during the retrieval of methamphetamine reward memory in rats (Shahveisi et al., 2019). Moreover, 6 h of total sleep deprivation at the beginning of the resting phase and after memory reactivation impaired the subsequent reconsolidation of morphine reward memory in male rats (Shi et al., 2011). Interestingly, in this same study, the authors found no effects of sleep deprivation on morphine reward memory retrieval and reward memory reconsolidation when sleep deprivation was carried out in the second part of the resting phase. These results suggest that sleep deprivation within a specific time window may facilitate the extinction of morphine reward memory but does not disrupt memory reconsolidation. The aforementioned studies explore how selective sleep deprivation can modify memory consolidation and extinction of drug associations that influence recovery, craving, and relapse.

Human studies have also reported that sleep loss induces changes in aversive emotional processing, including irritability, emotional volatility, anxiety, aggression, and suicidal thoughts and attempts (Krause et al., 2017). These changes in emotion are correlated with activity in brain areas involved in the processing of emotionally aversive stimuli. For example, one study reported a 60% greater magnitude of amygdala fMRI activity in response to negative stimuli in participants who experienced 35 h of total sleep deprivation, associated with a loss of functional connectivity with the mPFC, suggesting a failure of top-down control (Yoo et al., 2007). In line with these results, 4 h of sleep per night for five nights increased the activity of the left amygdala in response to the facial expression of fear and decreased the functional connectivity between the amygdala and the ventral anterior cingulate cortex (vACC), suggesting an impairment of the functional suppression of the amygdala again and consequently enhancing the response to negative emotional stimuli (Motomura et al., 2013). Similarly, during withdrawal, brain stress systems such as corticotropin-releasing factor, norepinephrine, and dynorphin are recruited in the extended amygdala and contribute to the development of negative emotional states with a deficient inhibitory process in prefrontal regions (Koob and Volkow, 2016). Taken together, sleep loss and withdrawal may enhance negative emotional states contributing to compulsive drug-seeking behavior and relapse.

Additionally, sleep deprivation has been shown to increase impulsivity while decreasing inhibitory ability (Frenda and Fenn, 2016), which may increase motivation for drug consumption. For example, seven days of total sleep restriction at the onset of the sleep phase increased alcohol consumption in rats (García-García et al., 2021). In

another study, rats deprived of sleep for 4 or 8 h during the resting phase increased motivation to self-administer cocaine. However, the incentive value of the drug was not modified, which was evidenced by an increase in rate infusion but a failure to significantly alter the progressive ratio responding to the drug (Puhl et al., 2009). And recently, mice deprived of sleep for the first 8 h of the light cycle, on the first three days of 4 consecutive weeks, did not showed enhanced morphine preference in voluntary intake; although, sleep deprivation did not affect conditioned reward (Eacret et al., 2022). These heterogeneous findings suggest that the type of sleep deprivation, its duration and timing, and drug dynamics need to be considered to determine the influence of sleep loss on motivation and drug consumption.

Sleep loss has been proposed to share plastic mechanisms with psychostimulant addiction, potentiating the dopaminergic system function. Therefore, behavioral sensitization is considered a pharmacological tool to examine plasticity in the mesolimbic dopaminergic circuitry that may underly drug craving and drug-seeking behavior. In mice, a period of 48 h of REM sleep deprivation potentiated amphetamine-induced behavioral sensitization (Frussa-Filho et al., 2004). These results were supported in another study in which 6 h of total sleep deprivation into the resting phase were shown to potentiate the hyperlocomotion effects of cocaine in mice (Berro et al., 2014a). However, further research found that responses elicited by amphetamine were potentiated by 6 h of total sleep deprivation into the resting phase but not by 6 h of REM sleep deprivation (Saito et al., 2014). Moreover, 4 h of total sleep deprivation into the resting phase influenced the development of locomotor sensitization to cocaine by inducing hypoactivity in response to the initial cocaine administration and increasing activity in subsequent cocaine administrations (Bjorness and Greene, 2018). These contrasting findings indicate that further research is needed to determine the conditions where sleep loss potentiates behavioral sensitization.

The neural mechanisms underlying all the changes attributed to sleep deprivation remain elusive. However, seminal studies reported that sleep-deprived animals show an augmented response to dopaminergic agents (Carlini, 1977; Carlini and Lindsey, 1974; Ferguson and Dement, 1969), suggesting that sleep deprivation induces supersensitivity of dopamine receptors (Tufik, 1981a, 1981b). Nevertheless, this hypothesis has been challenged by a series of experiments on animals and humans. For instance, four days of REM sleep deprivation did not increase post-synaptic D2 receptor number, and affinity was unchanged in rats' striatum and frontal cortex (Farber et al., 1983). Similarly, 72 h of REM sleep deprivation had no effect on D2 binding but decreased D1 receptors and increased D3 density in the striatum of mice (Lim et al., 2011). In a separate study, in rats, 96 h of REM sleep deprivation increased D2 but not D1 receptor binding in the NAc and caudate putamen (Nunes et al., 1994). Contrary, a pair of studies reported that 72 h of REM sleep deprivation increased the number of D1 receptors in rats' limbic system (NAc) (Demontis et al., 1990; Fadda et al., 1993). In humans, positron emission tomography showed that one night of sleep deprivation downregulated D2 receptors in the dorsal and ventral striatum (Volkow et al., 2012, 2008). Although inconsistent results have been obtained from dopamine receptors availability after sleep deprivation, decreases in D2 receptors could lead to the remaining D1 receptors becoming disproportionately stimulated. This imbalance is related to approach behavior and increases the addictive potential (Krause et al., 2017).

Additionally, sleep loss and substance abuse become significant during adolescence. Humans differ in their time of circadian preference or chronotype, which may vary from the extreme morning ("lark") type to the extreme nocturnal ("owl") type (Golombek et al., 2013; Roenneberg and Merrow, 2016). The impact of development on chronotype is evident in adolescents; during puberty, a preference for evening hours appears before a long and slow shift towards earlier hours in young adults (Duarte et al., 2014; Fischer et al., 2017; Karan et al., 2021). Coinciding with these changes, adolescents experience reduced sleep duration, increased daytime sleepiness, and sleep disturbances. Decreased sleep duration and increased sleep disturbance may result from delayed sleep timing and early morning school times during weekdays. Additionally, during the weekends, adolescents tend to stay up later creating a weekday-weekend shift in sleep and a circadian misalignment referred to as "social jet lag". Importantly, circadian misalignment and sleep disturbances/sleep lose during adolescence have been associated with increased substance use, earlier onset of substance use, and engagement in risky behaviors (Logan et al., 2018). In this sense, a recent work exploring the effect of the circadian disruption on alcohol consumption in rats reported increased alcohol consumption in the groups under shift time and accumulation of neural markers in corticolimbic structures (Reséndiz-Flores and Escobar, 2019). Similarly, rats under circadian disruption and exposed to methamphetamine showed a significantly higher percent change in methamphetamine consumption (Doyle et al., 2015).

4. Sleep loss and addiction: the relationship between orexin and reward circuit

The lateral hypothalamic area (LHA) is commonly labeled a feeding center associated with starvation or feeding behaviors. However, LHA activity has also been associated with motivation, reward, and cognition (Petrovich, 2018; Rossi and Stuber, 2018), among other physiological functions (Fakhoury et al., 2020). The LHA contains GABA neurons that project to the VTA (Sharpe et al., 2017), a dopaminergic center crucial for learning, reward processes, and feeding behavior. Furthermore, GABAergic outputs from LHA to GABA cells in the VTA trigger the disinhibition of Dopamine-VTA neurons, resulting in an increase of dopamine in NAc in mice; these effects were related to reward properties in real-time preference/avoidance and social interaction (Nieh et al., 2016).

Glutamatergic neurons from LHA also secretes a neuropeptide known as hypocretin, or orexin, that contains 33 (Orexin A) or 28 amino acids (orexin B) which bind to G-protein coupled orexin receptors type 1 (OX1R) and orexin receptor type 2 (OX2R) (Chieffi et al., 2017; Rosin et al., 2003), which are widely distributed throughout the brain and spinal cord, including LHA, prefrontal, and infralimbic cortex, hippocampus, and NAc among many other areas (Fakhoury et al., 2020; Marcus et al., 2001). The orexin is produced by proteolytic cleavage of a single precursor protein known as prepro-orexin (Sakurai et al., 1998).

Orexin-secreting neurons project from the LHA throughout the CNS to neurons involved in the regulation of feeding, neuroendocrine homeostasis, autonomic regulation, and specifically, to areas known for their role in promoting arousals like the cerebral cortex, basal forebrain, VTA, tuberomammillary nucleus (TMN), locus coeruleus (LC), and dorsal raphe nucleus (DR) (Peyron et al., 1998).

The orexin signaling is emerging as necessary for motivated psychostimulant seeking, elicited by external triggers like drug-associated cues. Such triggers are known to elicit craving and relapse behavior, and this may reflect a role for the orexin in conditioned responding to highly salient rewards. Therefore, an increase of OX1R signaling and thereby enhancing VTA dopamine responses is proposed as an inducer of craving response (James et al., 2017). Currently, there is a lot of evidence that shows the role of the ORX neurons associated with reward and drug consumption (Table 2).

In addition, manipulation of orexin receptors modulates drug seeking and drug intake in lab rodents (see Matzeu and Martin-Fardon, 2022 for a review). Orexin receptors have a significant density in the VTA (Marcus et al., 2001). The acute activation of orexin neurons of the LHA projecting to VTA increases food and drug reward-seeking behavior (España et al., 2010; Harris et al., 2007, 2005; Narita et al., 2006; Zheng et al., 2007).

On the other hand, suvorexant, an orexin receptor antagonist used to treat insomnia and sleep disorders, improved sleep, and reduced cocaine craving (Suchting et al., 2020); suvorexant has also been considered a potential option treat alcohol- and opioid-use disorder (Campbell et al.,

Table 2
Role of the ORX neurons associated with reward and drug consumption.

Main finding	References
The first study that shown that orexin neurons are related to addiction. The authors showed that orexin neurons in mice have mu-opioid receptors and respond to chronic morphine administration and opiate antagonist-precipitated morphine.	(Georgescu et al., 2003)
Orexin neurons discharge in active waking and have moderate and approximately equal activity levels during grooming and eating and maximal activity during exploratory behavior. These results suggest that orexinergic activity is linked to motivating behavior.	(Mileykovskiy et al., 2005)
Orexin neurons are directly related to reward and addictive behavior. The administration of the orexin-A peptide into the ventral tegmental area reinstated drug-seeking.	(Harris et al., 2005)
Orexin strengthened presynaptic glutamatergic inputs to VTA only in cocaine or high fat self-administering rats. This result supports that orexin signaling is related to motivation for highly salient reinforcers	(Borgland et al., 2009)
Pleasurable activities in dogs, like playing, increase orexin levels in the brain. Potentially, emotional aspects play a primary role in the synthesis of orexin.	(Wu et al., 2011)
Orexin KO mice are deficient in the performance of positively reinforced tasks. These suggest the primary role of the orexinergic system in reinforcement mediated by pleasure activities.	(McGregor et al., 2011)
Orexin neurons modulate abuse substance consumption and feeding behavior mediated by palatable food. These suggest compulsive-seeking behaviors may be regulated by the orexinergic system.	(Feillet et al., 2017)
Orexinergic reward neurons have a characteristic electrical activity compared to arousal neurons. According to electrophysiological studies, orexin neurons may respond to and participate in reward processes by modulating cortical and muscle tone in adaptative behavioral responses.	(Hassani et al., 2016)
The firing of the orexin neurons is correlated with alcohol seeking and preference.	(Lawrence et al., 2006; Moorman et al., 2016)
It is proposed that the orexin system can be a pharmacological target to reduce addiction-like behaviors.	(James et al., 2017)
Experimental studies have been shown drug-seeking behavior was primarily modulated by orexin-1-receptor. Potentially antagonist to this receptor can effectively attenuate addiction to abuse substances in rats.	(Fragale et al., 2019; Matzeu and Martin-Fardon, 2020)
Long-term administration of morphine in mice increases orexin neurons; these findings were previously observed, in human heroin addicts. These results suggest that orexin neurons are responsible for maintaining addiction.	(Thannickal et al., 2018)
According to several experiments carried out in mice and rats, the number of LH orexin neurons could be considered a biomarker of addiction or susceptibility.	(James et al., 2019; Pantazis et al., 2020)
Agonism of group III metabotropic glutamate receptors (mGluRs) reduces presynaptic glutamate release onto orexin cells, consequently, the hyperactivity of orexin cells during abstinence could reduce the risk of relapse.	(Yeoh et al., 2019)
Intermittent access to cocaine is accompanied by an increase in the number and activity of orexin-expressing neurons on the lateral hypothalamic. Interestingly, this increase persisted during the withdrawal period. Experimentally has been demonstrated that blocking or antagonisms of orexin-1-receptor might be a pharmacological target to treat cocaine addiction.	(James et al., 2019)

2020; James et al., 2020). In addition, the orexin properties have led to propose of the orexin system as "a potential neurobiological link between drugs of abuse and co-occurring eating and sleep dysregulations" (Matzeu and Martin-Fardon, 2022) and a target for therapeutic effects on addiction (Fragale et al., 2021).

Recent studies showed that blocking OX1R abolishes alcohol, cocaine, opioids, and nicotine consumption in rodents (Lei et al., 2016; Smith and Aston-Jones, 2012). The orexin has a pivotal role in waking induction in mammals; for that reason, it is plausible to suggest that sleep disruption induces an increase in orexin levels that potentially excite neurons related to waking regulation, for example, histaminergic neurons from TMN or noradrenergic neurons from LC. The VTA is also part of the brain circuit associated with waking induction (Eban-Rothschild et al., 2020, 2016; Oishi and Lazarus, 2017; Yu et al., 2018). VTA DA neurons are activated by ORX in vitro (Korotkova et al., 2003) and in vivo (Muschamp et al., 2007; Vittoz et al., 2008), and ORX intracerebroventricularly or in VTA increases DA release in PFC and NAc (Narita et al., 2006; Vittoz and Berridge, 2006). These brain areas are part of the rewarding system associated directly with drug consumption. Therefore, we hypothesized that chronic sleep disruption increases orexin signaling and stimulates VTA neurons to stimulate the reward system (Fig. 1).

Recently, our group showed that sleep restriction of 4 h for seven days increased the total number of delta FosB positive cells in the VTA (García-García et al., 2021). The gradual accumulation of delta FosB strengthens the formation and maintenance of habit memories and compulsive behaviors, perhaps by reinforcing the efficacy of neuronal circuits in which those neurons work (Nestler et al., 2001). Therefore, the accumulation of delta FosB in the VTA indicates that sleep loss increased neuronal activity of the VTA neurons. The evidence indicates that glutamate neurons in the VTA increase wakefulness. Optic stimulation of glutamate fibers from the VTA to the LH and NAc promotes waking from NREM sleep and increases wakefulness (Yu et al., 2018). Therefore, the role of the VTA in reinforcing and goal-directed behaviors links this region directly to wakefulness. However, experiments are needed to strengthen the role of the VTA in the induction of wakefulness beyond its relationship with the reward behaviors inherent in wakefulness.

The dopamine from VTA neurons affects GABAergic neurons of the NAc. The spiny medial neurons of the NAc send projections to PFC, ventral pallidum, substantia nigra, and pontine reticular formation; these circuits then elicit positive behavior during reward (Han et al., 2017). Hypothetically, recurrent activation of the VTA neurons due to lengthening of wakefulness potentially produces hyperstimulation of the rewarding system; as a result, the system is sensitive to drug consumption (Fig. 1). It is well known that stimulant drugs that increase dopamine concentrations are potent wakefulness promoters (Boutrel and Koob, 2004). Previous studies report that one night of sleep deprivation in humans increases striatal DA and produces striatal hyperstimulation of D2 receptors (Volkow et al., 2008). However, for 72 h in mice, sleep deprivation did not affect D2 receptors (Lim et al., 2011). In this sense, Volkow and co-workers (2008) suggest that striatal DA increases may reflect a counteracting effect to maintain arousal as the drive to sleep increases. Thus, greater extended wakefulness would significantly increase striatal DA. Therefore, continuous sleep restriction produces a neurochemical imbalance between DA, DA receptors, and orexins. These alterations together make the brain vulnerable to drugs.

D2 receptors are coupled to Gαi/o to inhibit adenylate cyclase and calcium channels, activate inhibitory G-protein and activate inwardly rectifying potassium channels (GIRK) (Beaulieu and Gainetdinov, 2011; Neve et al., 2004). D2 receptors are found at a high density in the striatum, NAc, and olfactory tubercle, and to a lower extent in the hippocampus, amygdala, hypothalamus, and cortical regions (Beaulieu and Gainetdinov, 2011; de Mei et al., 2009; Missale et al., 1998; Schmitz et al., 2003). D2 receptors are found on the terminals of dopamine neurons and post-synaptically on non-dopamine neurons

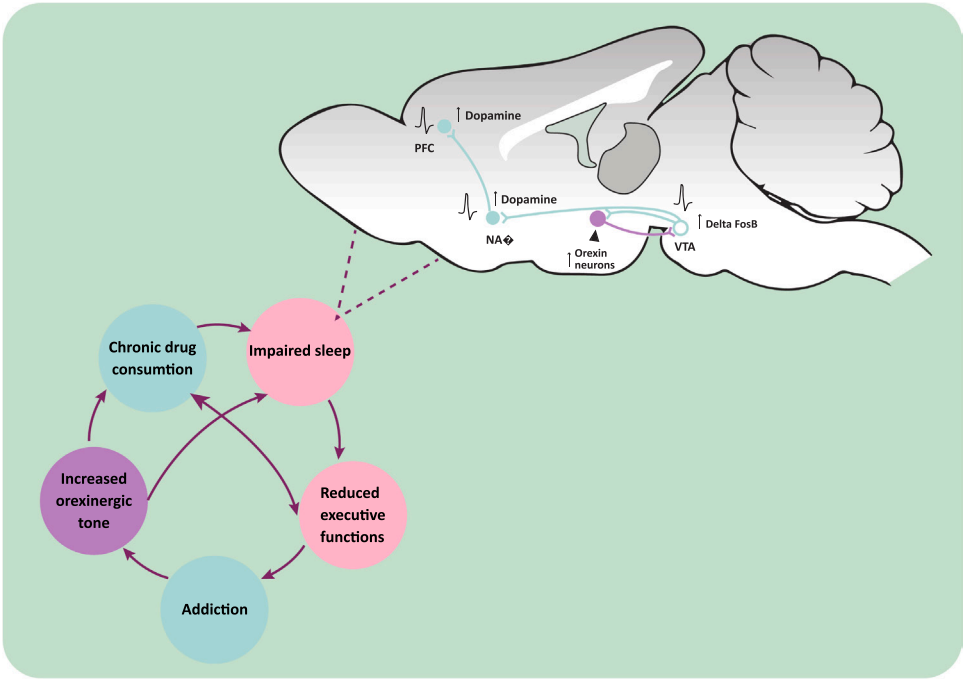

Fig. 1. Chronic sleep restriction (CSR) generates an overstimulation of the orexinergic system, which stimulates the reward circuit (VTA, NAc, PFC), inducing dopamine release, receptor sensitization, and delta FosB expression. According to Fragale et al. (2021) insomnia caused by elevated orexin also degrades executive function, which compromises attempts at drug abstinence. As a result, chronic drug consumption leads to poor sleep quality; consequently, individuals with sleep disorders intake drugs such as alcohol, cocaine, opioids, etc., to improve sleep quality, leading to addiction.

(heteroreceptors). D2 autoreceptors knock out mice show inhibition of dopamine release from dopamine terminals and hyperpolarization measured in the cell body (Anzalone et al., 2012; Bello et al., 2011). Interestingly, these animals are hyperactive and exhibit increased sensitivity to cocaine (Anzalone et al., 2012; Bello et al., 2011). This supports the role of D2 autoreceptors in regulating locomotor and reward-driven behaviors (Ford, 2014).

Additionally, preferential components must be considered when studying sleep loss or sleep restriction in humans; in other words, sleep deprivation is usually due to an individual's willingness since pleasurable activities can accompany it. However, animal models do not reflect this willingness, and sleep restriction is generally imposed or forced generating stress; perhaps intracranial self-stimulation (ICSS) deprivation models (Oonk et al., 2016) could be used to take into account the hedonic components involved in this phenomenon. This important difference could be crucial at the neuronal and molecular levels and remains and issue to be explored. For example, it has been shown that sleep deprivation can increase the expression of genes involved in neuronal structural changes, for example, *Arc*, phosphorylated proteins such as pCREB, or neurotrophic factors such as the brain-derived neurotrophic factor (BDNF) in the cortex, hippocampus, or in noradrenergic regions (Cirelli and Tononi, 2000; Seibt and Frank, 2019).

Drug use has been shown to induce neuronal plasticity; for example, by increasing the expression of delta FosB protein, the gene for Cdk5, which is involved in the production of dendritic spines, or by increasing the production of the GluR2 subunit of AMPA glutamatergic receptors (Nestler, 2001; Nestler et al., 2001), and sleep deprivation can induce the expression of immediate early genes (IEGs) (Seibt and Frank, 2019). However, there is a lack of studies on what neural plasticity, sleep deprivation and drug use, can cause in brain regions such as the dopaminergic system.

It is known that plastic mechanisms can initially be dependent on experience and independent of gene translation through protein phosphorylation and expression of IEGs. After this, there are changes dependent on gene translation, which involve covalent changes in proteins. It is hypothesized that this last process could be reinforced in sleep, particularly during REM sleep. Hypotheses have been proposed through explanatory models such as metaplasticity, which suggest that the plastic changes generated during experience could be favored and strengthened in sleep, to later be wholly consolidated in wakefulness, as a process of plastic consolidation sleep which requires wake-sleep-wake periods (Seibt and Frank, 2019).

These studies show that the findings on sleep deprivation and drug use in animal models are not as abundant and consistent, and the majority have focused on the early plastic changes. Given this, experiments in which the plastic mechanisms are allowed to consolidate after periods of waking-sleep-waking or looking for marking processes, labeling of circuits and synapses (synapsis tagging), for example, looking for changes in protein phosphorylation, increase in transcription factors, or changes in cytoskeleton components involved in synaptic remodeling such as actin filaments. Specifically, in the face of sleep deprivation and the consumption of addictive substances, products related to plasticity such as neurotrophins, BDNF, AMPAR subunit GluR1, or PKMzeta could be sought, along with a behavioral explanation.

5. Conclusions

In summary, results from human and animal studies regarding the relationship between sleep loss and substance abuse are still heterogeneous and even contrasting in some cases. Thus, some topics must be considered in the research agenda, for example:

1. The nature of the rewarding stimuli (sedatives, stimulants, and behavioral addictions).
2. The influence of sleep stages (REM and NREM); the differences between total sleep deprivation, sleep restriction, and sleep disruption/fragmentation protocols, as well as the length of the experimental protocol on every stage of the process of addiction (i.e., bingeing, withdrawal, craving).
3. The influence of sleep loss in memory consolidation, extinction, and the association between contextual cues and rewarding effect of drugs that influence recovery, craving, and relapse.
4. The influence of sleep loss on aversive emotional processing and the interaction between sleep loss and withdrawal.
5. The effect on neural plasticity. Changes in the mesolimbic dopaminergic circuitry and dopamine receptors remain to be elucidated. Besides, both sleep loss and drug use induce the expression of genes

involved in neural changes (i.e., Arc, pCREB, BDNF, Cdk5, FosB), which are consolidated in wake-sleep-wake periods.
6. The influence of wake-promoting neurotransmitters like orexin and dopamine, and their interaction, on reward processing.

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Author contribution

All authors have contributed substantially to the drafting of the work, revised data set and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Data Availability

No data was used for the research described in the article.

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