Delayed circadian rhythms and substance abuse: dopamine transmission's time has come

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Disrupted sleep and circadian rhythms are linked with substance abuse risk. Human studies that investigate relationships between sleep, circadian rhythm, and substance use reward generally rely on indirect means to infer dopaminergic function, such as functional magnetic resonance imaging. In this issue of the *JCI*, Zhang and colleagues used positron emission tomography (PET) to image striatal dopamine D1 (D1R) and D2/3 receptor (D/3R) availability in healthy adults. The authors assessed rest-activity rhythms, then conducted PET scans using radioligand antagonists selective for D1 receptors or D2/D3 receptors to measure D1R and D2/3R availability. They also measured the subjective drug effects of oral methylphenidate. Higher D1R availability in caudate and a greater methylphenidate reward sensitivity were associated with delayed rest-activity rhythms. Unexpectedly, lower overall activity was associated with higher D2/3R availability in the nucleus accumbens, which coincided with greater methylphenidate reward score. These findings may inform personalized prevention and/or treatment interventions.

Linking sleep/circadian rhythm phenotypes with drug reward

Disruptions in circadian rhythms and sleep have been increasingly linked to substance abuse risk (1). Along with insomnia and insufficient sleep, a circadian preference for eveningness (tendency toward later sleep/wake timing) and delays in sleep timing have been associated with increased substance use and substance-related problems (2). Preclinical and human studies indicate that altered function in the mesolimbic neurocircuitry underlying reward function may partly account for these sleep/circadian and substance use associations. For example, a recent functional magnetic resonance imaging (fMRI) study found that people with tendency toward eveningness had increased ventral striatal and prefrontal responses to monetary reward wins, the latter of which correlated with greater symptoms of alcohol dependence (3). However, to date, most human studies investigating sleep/circadian reward–substance use pathways have been limited to fMRI methodology, and thus unable to directly examine whether apparent variations in reward processing are related to dopaminergic function.

In this issue of the *JCI*, Zhang et al. (4) take an important next step in teasing apart some of the potential mechanisms that link sleep and circadian rhythm phenotypes with drug reward. The authors leverage positron emission tomography (PET) neuroimaging of striatal D1 (D1R) and D2/3 receptor (D/3R) availability in order to investigate whether sleep or circadian characteristics previously linked to substance use are associated with variations in dopaminergic function. They recruited a cohort of 32 healthy adults (middle-aged on average) and assessed rest-activity rhythms (24-hour patterns of rest and activity) using wrist actigraphy, as well as sleep timing and duration based on actigraphy and self-report, over one week. The researchers then conducted PET scans using radioligand antagonists selective for D1 receptors or D2/D3 receptors to measure D1R and D2/3R availability. Importantly, the authors also measured the subjective drug effects of experimentally administered oral methylphenidate. Since previous studies from this research group and others have found that higher striatal D1R and lower D2/3R availability generally associate with increased vulnerability to substance use (5), the authors hypothesized that delayed and weaker or more irregular rhythms would correlate with higher D1R and lower D2/3R availability, as well as greater sensitivity to the rewarding effects of methylphenidate. In support of their hypothesis, Zhang et al. found that higher D1R availability in caudate and greater sensitivity to the rewarding effects of methylphenidate were associated with delayed rest-activity rhythms based on wrist actigraphy. Interestingly, this association was independent of sleep duration, which is important as it underscores that the timing, not just the amount of sleep, has important implications for the function of the dopaminergic reward circuitry. In the past, many researchers have assumed that any changes seen in association with circadian rhythm disruption were likely due to a lack of sleep. However, more recent studies have challenged this idea and found that the timing of sleep and other daily activities can have profound effects on a number of physiological processes independent of sleep duration (6, 7).

Circadian misalignment and social jet lag

Several studies in the past have suggested that associations between delayed circadian phase and factors like depression, reward seeking, and increased substance

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use might be due to the struggle that late sleepers have in adapting to imposed academic or work schedules that are too early for their biological rhythms, leading to circadian misalignment. This misalignment often manifests behaviorally as a marked difference between sleep timing in school/work days versus free days, which has been termed social jet lag (8). Social jet lag has been linked to altered reward function (9) and, in some but not all studies, increased substance use (10, 11). A recent fMRI study that experimentally imposed circadian misalignment in healthy adolescents found an alteration in ventral striatal response to reward, supporting the idea that misalignment between delayed rhythms and environmentally imposed early sleep timing can impact reward circuitry (12). The finding that the association between delayed phase and D1R availability in the caudate is independent of social jet lag is, consequently, very interesting. It is possible that the genetic factors that lead to delayed rhythms either travel together with factors that influence dopaminergic function, or that a delay in the molecular clock itself regulates both dopaminergic function and sleep/wake preference, either in an interacting pathway or in parallel. Several preclinical studies in mice have found that the core molecular clock directly regulates multiple genes involved in dopaminergic transmission, such as tyrosine hydroxylase, dopamine transporter, monoamine oxidase A, and dopamine D3 receptor (13). Extracellular dopamine levels also display a strong diurnal rhythm in striatal regions, which are controlled by rhythms in dopamine transporter function (14). Importantly, similar to the delayed sleepers in Zhang et al. (4), mice with a mutation in the core circadian gene, *Clock,* have delayed activity rhythms, which are associated with increased dopaminergic transmission in the striatum and increased reward value for drugs of abuse (15, 16). These results suggest that the variation in D1R availability and the delayed activity rhythms in humans are both due to direct effects of the molecular clock. Future studies will need to determine how intertwined these processes are and if one follows the other. For example, do delayed activity rhythms feed back to the dopamine system or do changes in dopaminergic transmission influence sleep/wake patterns? Or are these systems perhaps parallel processes, both controlled locally by their own core molecular clock, independent of each other?

Reward and motivation

Surprisingly, Zhang et al. (4) found that less daily activity as well as a lower relative amplitude in the rest-activity rhythm (based on nonparametric circadian rhythm analysis) were associated with higher D2/3R availability in the nucleus accumbens (NAc). This higher D2/3R availability also associated with greater reward value for methylphenidate. Both findings were unexpected given that past studies have found that lower D2/3R availability increases risk for substance abuse (17). Interpreting the present findings (4) is complicated by the study's use of physical activity and exercise as a proxy for activity rhythms, as exercise on its own can influence the dopamine system, particularly in the NAc (18). Thus, it is unclear if these results are related to blunted rhythms per se, or differences in physical exercise. However, they do highlight the interplay between these factors in the NAc and need for further study. Future studies can use other measures of circadian phase and amplitude, including measures of dim light melatonin onset, core body temperature, rhythms, or molecular rhythms in skin or peripheral samples to disentangle the effects of exercise and activity rhythms versus variations in core circadian rhythms.

It is intriguing that the association between delayed rhythms and D1R receptor availability occurred in the caudate, while the D2/D3R availability increase with blunted rhythmicity took place in the NAc (4). The caudate is primarily engaged in cognitive and executive processes while the NAc associates more with reward and motivation (19). As eveningness (indicated as delayed timing) has been consistently associated with trait-level impulsivity (20–22), it is possible that greater D1R availability in the caudate results in increased impulsivity, which creates vulnerability for substance use. Increased D2/D3R availability in the NAc is likely to be involved primarily in drug reward sensitivity. As noted in Zhang et al. (4), the D2/D3R results conflict to some extent with other studies that generally find an association between lowered D2/D3R availability and the rewarding properties of drugs, though these associations are somewhat specific to the type of substance studied. Future studies are needed to determine the cause of these discrepancies across studies. Such studies could involve a variety of factors, including age, which Zhang et al. note may contribute to mixed D2/D3R findings. It would be valuable to investigate dopaminergic signaling in a younger sample, especially given that the tendency toward delayed sleep/circadian timing peaks during late adolescence and emerging adulthood, and substance abuse often first emerges during this time (1). Sex and race effects will also be important to consider, given that emerging evidence suggests that they may influence the association between sleep/circadian characteristics, substance use patterns, and response to substances (23–25).

Conclusions and clinical implications

There are multiple clinical implications for these studies. First, the authors suggest that there is value in developing personalized prevention and/or treatment interventions that take into account the particular circadian profile of an individual. For example, someone who has an advanced phase in rhythmicity might have very different dopaminergic signaling properties compared with someone who has a delayed phase, thus they might require a different type of treatment for substance use disorders. Since we know that individuals with a delayed phase seem to be at higher risk for substance use, there is also the possibility for interventions that target the circadian system to modify dopaminergic signaling and reestablish proper reward-related function. Such chronotherapeutic interventions including bright light, blue light–filtering glasses, melatonin, and sleep scheduling have already been demonstrated to correct circadian misalignment associated with delayed phase (26), but their benefit for normalizing reward function and mitigating substance abuse risk remain unproven. Adolescents who tend to have a delayed phase and are particularly vulnerable for substance abuse may benefit from chronotherapeutic intervention. Similarly, the timing and duration of exercise may help to maximize the impact on substance use

prevention and relapse. Future studies can build upon these important findings to further explore mechanistic links and translate results to the clinic.

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