

REVIEW

Dopamine Signaling in Circadian Photoentrainment: Consequences of Desynchrony

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Circadian rhythms, or biological oscillations of approximately 24 hours, impact almost all aspects of our lives by regulating the sleep-wake cycle, hormone release, body temperature fluctuation, and timing of food consumption. The molecular machinery governing these rhythms is similar across organisms ranging from unicellular fungi to insects, rodents, and humans. Circadian entrainment, or temporal synchrony with one's environment, is essential for survival. In mammals, the central circadian pacemaker is located in the suprachiasmatic nucleus (SCN+) of the hypothalamus and mediates entrainment to environmental conditions. While the light:dark cycle is the primary environmental cue, arousal-inducing, non-photic signals such as food consumption, exercise, and social interaction are also potent synchronizers. Many of these stimuli enhance dopaminergic signaling suggesting that a cohesive circadian physiology depends on the relationship between circadian clocks and the neuronal circuits responsible for detecting salient events. Here, we review the inner workings of mammalian circadian entrainment, and describe the health consequences of circadian rhythm disruptions with an emphasis on dopamine signaling.

INTRODUCTION

Circadian rhythms regulate biological processes ranging from gene expression to behavior. The period, amplitude, phase, and waveform of these oscillations are governed by an internal clock that has evolved in a variety of organisms to anticipate events such as sunrise and sunset [1,2]. Proper phase alignment of the circadian

pacemaker to environmental timing cues is critical for an organism's well-being and survival. Darwinian pressures have changed for humans as many of the emergent stressors of modern society burden our ancient circadian physiology. Varying environmental conditions experienced during shift work or transmeridian travel create desynchrony between the time of day and the internal clocks [3]. Additionally, inappropriately timed light exposure

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†Abbreviations: AAV, Adeno-associated virus; AVP, Arginine vasopressin; ChR2, Channelrhodopsin; Cre, Cre recombinase; CT, Circadian time; DA, Dopamine; DD, Constant darkness; DIO, Double inverted open reading frame; Drd1, D1 dopamine receptor; Drd2, D2 dopamine receptor; FEO, Food entrainable oscillator; GABA, Gamma-Aminobutyric Acid; HFD, High-fat diet; ipRGC, intrinsically photosensitive retinal ganglion cell; KO, Knockout; LD, Light:dark cycle; LD, Light-dark; MA, Methamphetamine; MASCO, Methamphetamine entrainable oscillator; NMS, Neuromedin S; NPY, Neuropeptide Y; PACAP, Pituitary adenylate cyclase-activating polypeptide; SCN, Suprachiasmatic nucleus; VIP, Vasoactive intestinal peptide; VTA, Ventral tegmental area; ZT, Zeitgeber time.

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from portable hand-held devices present a chronic source of circadian and sleep disruptions [4]. When prolonged, such misalignments result in higher incidences of mood disorders, obesity, cardiovascular disease, and cancer [5]. As such, pathologies associated with circadian dysfunction are increasing at an alarming rate, creating the pressing need to better understand the basis of circadian physiology in order to advance the practice of psychiatry, nutrition, and medicine [6,7].

While the endogenous circadian clock remains functional in constant conditions [8-10], it relies on environmental signals (*Zeitgebers*) to synchronize the organism's physiology to daily external rhythms, such as the earth's 24-hour light:dark (LD) cycle. As reviewed in [11], the synchronization of an organism's internal rhythms to an external cycle, termed entrainment, requires the molecular clock machinery to align endogenous rhythms with the exogenous daily cycles. In mammals, entrainment by light, termed photoentrainment, is mediated by the light-activated neural circuits originating in the retina that project to the suprachiasmatic nucleus (SCN) through the retino-hypothalamic tract [12-14]. Non-image-forming, irradiance information is primarily transmitted to the SCN by the melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs) [15-18]. Located in the basal hypothalamus dorsal to the optic chiasm, the SCN orchestrates rhythms throughout the rest of the brain and body as described in the following reviews [19-21]. The diverse cellular components of the SCN are both necessary and sufficient for circadian rhythm maintenance as surgical ablation of this nucleus produces behavioral arrhythmia, while grafts of neonatal SCN into a SCN-ablated host restores rest-activity rhythms [22-24].

For proper adaptation to a dynamic world, this circadian timing system also requires the ability to anticipate salient events such as food or mate availability. While light is the primary entraining agent, arousal-inducing non-photic cues such as palatable foods, social interaction, and physical exercise also influence the phase of the SCN molecular clock [25,26]. Dopamine (DA), a neurotransmitter mostly known for its role in reward processing and motivation, is a significant modulator of the aforementioned behaviors that drive non-photic circadian entrainment [27,28]. Additionally, patients suffering psychiatric and neurodegenerative pathologies associated with DA signaling dysregulation such as depression, bipolar disorder, schizophrenia, drug addiction, and Parkinson's disease are known to have perturbations of circadian rhythms [29-33]. As such, DA is emerging as an important regulator of central and peripheral circadian rhythms and has been reviewed in the following publications [34,35]. In this review, we focus on how DA-mediated neural circuits influence our daily rhythms and the attendant consequences of circadian misalignment on

well-being, metabolism, and mental health.

NON-PHOTIC ENTRAINMENT

The regulation of circadian entrainment is accomplished through various neuropeptides and neurotransmitters such as: vasoactive intestinal peptide (VIP), arginine vasopressin (AVP), neuromedin S (NMS), glutamate, gamma aminobutyric acid (GABA), serotonin, Neuropeptide Y (NPY), and DA [36-40]. In addition to retina-dependent photoentrainment, light-independent neural circuits likewise directly influence SCN neurons to regulate circadian phase. The most prominent non-photic entrainment cues in mammals are behavioral arousal induced by sleep deprivation, animal handling, or exposure to a novel running wheel [41,42]. Serotonin and NPY are known to directly change SCN molecular rhythms and induce phase shifts of circadian activity during the subjective day, when the SCN is least sensitive to light and most sensitive to non-photic entrainment cues [43-46]. However, the precise mechanism of phase-resetting by behavioral arousal remains unknown. Below we discuss the potential involvement of dopamine signaling in mediating these behaviors and highlight several connections between changes in DA tone and circadian entrainment.

DOPAMINE SIGNALING AND CIRCADIAN RHYTHMS

Dopamine, a monoamine neurotransmitter well known for its role in reward and motivation, is also important for the detection of salient events such as food or mate availability [28,47-49]. To facilitate a myriad of physiological and behavioral outputs, DA modulates neural activity through a group of G-protein coupled receptors distinguished by their cognate G-proteins—G_s-coupled (D1 and D5), and G_i-coupled receptors (D2, D3, D4)—that are expressed in anatomically distinct regions throughout the brain and body [50-52]. Importantly, DA signaling associated behaviors such as drug self-administration, food reward, and mating all fluctuate in the extent of their expression across the day:night cycle revealing an association with circadian regulation [34,53,54]. Having a well-coordinated neuronal communication between the dopaminergic and circadian systems is likely necessary for appropriately timed behavioral responses, adaptation to the environment, and survival.

The bi-directional nature of this link has gradually been uncovered in the last few decades. DA synthesis, release, and signaling within the retina, olfactory bulb, ventral tegmental area, and striatum are all regulated in a circadian manner [55-58]. DA has been shown to directly alter clock gene expression within extra-SCN circadian oscillators [59-61]. Early studies in *Xenopus* revealed an

important role for DA in the entrainment of retinal circadian rhythms whereby *Per2* expression, a core molecular component of the circadian clock, is induced in response to both light and DA [59,62]. Similarly, activation or inhibition of the D1 dopamine receptor (*Drd1*) in the mammalian retina enhances or attenuates the extent of light induced phase shifts, respectively [60]. Additionally, D2 dopamine receptor (*Drd2*) null mice have significantly diminished suppression of wheel running activity by light [63]. Taken together these data support that DA signaling outside of the central pacemaker is an important mediator of circadian regulated behaviors.

Midbrain dopaminergic neurons of the ventral tegmental area (VTA) and substantia nigra (SN) are particularly relevant to DA-induced behavioral modification due to their involvement in locomotion, addiction, and reward recognition [64-66]. Additionally, the expression of circadian clock genes such as *Per*, *Clock*, and *Bmal1* are found within both neuronal populations suggesting a molecular link to circadian regulation [54,67-69]. Selective manipulation of VTA neurons regulates sleep-wake states by promoting salience-induced arousal, enabling the regulation of ethologically relevant behaviors [70]. Lesioning the VTA of rats with 6-hydroxydopamine treatment has been shown to elongate circadian free-running period, alter the onset of drinking behavior, and decrease wheel running activity rhythms [71]. These changes in circadian behavior following alteration of the mesolimbic DA system further highlight the significant interaction between these two systems. Additionally, the striatum, a midbrain DA-neuron projection site important for learning, reward, and motor control, has been shown to exhibit rhythmic circadian clock gene expression [72,73]. Within this brain region, depletion of DA innervation and pharmacological inhibition of *Drd2* signaling disrupts the expression profile of *Per2*, implicating a role for circadian regulators on reward driven processes [61,67]. This is further supported by the evidence that *Per2* mutant mice exhibit heightened sensitivity to cocaine [53]. A complete understanding of how DA influences these extra-SCN oscillators will provide important insight into how substance abuse or neurodegenerative disorders that impact the dopaminergic system are able to disrupt circadian rhythms. The link between these two systems is briefly described below and detailed in the following manuscripts [74-76].

When the SCN is compromised, nearly all circadian functions disappear [23]. However, non-photostimuli such as restricted food access or chronic exposure to methamphetamine (MA) can restore rhythmic behavior in SCN lesioned animals. Interestingly, these SCN-independent pacemakers of unknown origin are modulated by the dopaminergic system, which likely mediates additional biological oscillations and their entrainment [77-80]. For instance, scheduled feeding during a restricted

portion of the day produces increased locomotion prior to the availability of food, a behavior known as food anticipatory activity (FAA) [79,81,82]. FAA persists even after SCN ablation, suggesting the presence of an independent food entrainable oscillator (FEO) [41,83-85]. The dorsal striatum has been implicated as a mediator of FAA, while *Drd1* null mice demonstrate reduced FAA implicating DA-*Drd1* signaling as a modulator of this important anticipatory behavior of food availability [79,86].

Similar to anticipation of food reward, daily administration of MA, a DA enhancing psychostimulant, increases locomotor activity immediately preceding the time of injection [87]. Strikingly, arrhythmic SCN-lesioned animals regain circadian rhythmicity via a methamphetamine-sensitive circadian oscillator (MASCO) when presented with *ad libitum* access to MA in their drinking water [77,80]. Furthermore, a recently described dopaminergic ultradian oscillator (DUO) was found to produce aberrant patterns of arousal when DA tone was elevated through selective activation of the VTA [78]. While these extra-SCN oscillators can compensate for a compromised SCN-based clock, it is possible that DA signaling also directly influences the intact SCN to relay information about salient events such as food or mate availability.

DOPAMINE IN THE SCN

Almost 30 years ago, DA signaling within the embryonic SCN was first demonstrated to synchronize maternal-fetal circadian rhythms. Administration of dopaminergics to pregnant dams induced *c-fos* mRNA-expression, a marker for neural activity, within the fetal SCN, while periodic injections of a *Drd1* agonist were shown to set the phase of the fetal biological clock [88,89]. These treatments fail to induce molecular changes within the SCN of the *Drd1* null mice, confirming the importance of this G_s-coupled receptor in mediating the effects of DA on the circadian axis [90]. Despite persistent expression of SCN-*Drd1* mRNA in adult rodents, baboons, and humans, administration of *Drd1* agonist alone is not sufficient to induce *c-fos* mRNA expression within the SCN or induce behavioral phase shifts of free running animals after postnatal development [91-93]. Based on these findings, it was concluded that sensitivity to DA signaling within the SCN is transient and is lost after the development of the retinohypothalamic tract [91,94]. However, recent advances in mouse genetics, designer actuators, and viral vector technologies have enabled investigators to challenge that notion and develop a more complete understanding of how *Drd1*-mediated DA signaling directly modulates the central circadian clock throughout adulthood.

Drd1-expressing neurons represent approximately 60 percent of the cells within the SCN, including partial

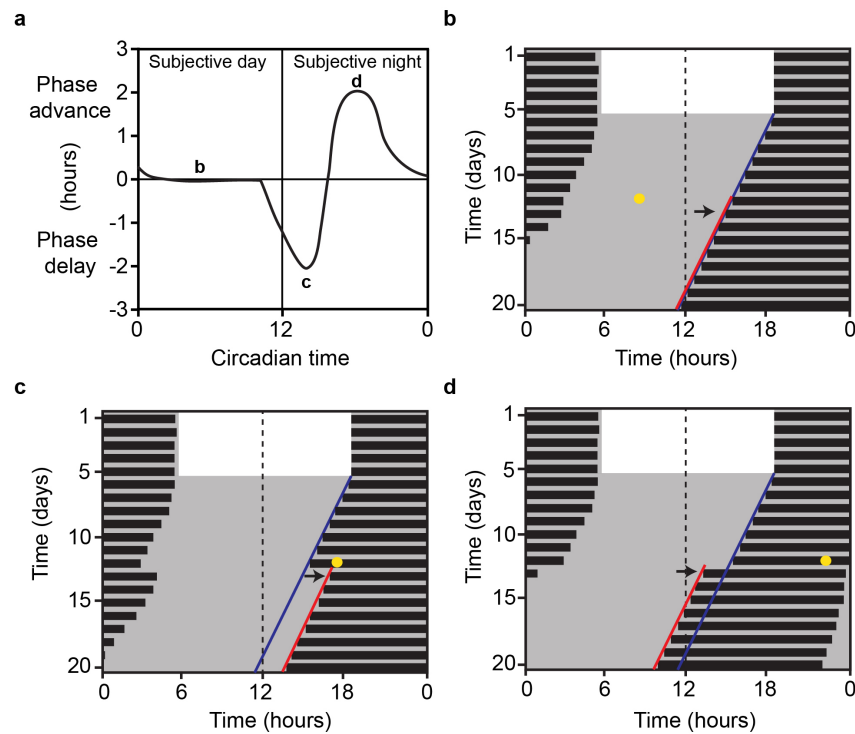


Figure 1. Phase response curve of circadian rhythms to light. **a.** Illustration of the photic PRC in mice. By convention, phase advances are recorded as positive values and phase delays as negative. Plot of wheel running actograms representing the locomotor response of to a brief light pulse during the **b.**, subjective day, **c.**, early subjective night (inducing a phase delay), and **d.**, late subjective night (inducing a phase advance). Black bars represent wheel running activity; yellow dots indicate time of light pulses in DD; dark blue lines represent an extended regression line derived by activity onsets prior to the light pulse; red lines follow actual onset of activity after the light pulse. The duration of phase shift is quantified as the horizontal difference between the two regression lines on the day after the light pulse marked by the black arrows [40].

overlap with NMS, VIP, and AVP-expressing neurons [95]. Acute treatment of mouse SCN explants with the Drd1 agonist, SKF 38393, lengthens the free running period of circadian molecular rhythms, suggesting that DA signaling remains functional in the adult SCN [96]. Use of advanced genetic tools has recently identified the behavioral phase and period-resetting properties of Drd1-expressing neurons within the adult mammalian SCN [40,95,97]. Optogenetic stimulation of channelrhodopsin (ChR2)-expressing Drd1-SCN cells is sufficient to entrain free-running mice to the time of stimulus [97] in a similar manner to the entrainment capacity of a scheduled palatable snack [98-100]. This finding is significant because an entrainable circadian pacemaker requires resetting by which the intensity, duration, and phase of the applied stimulus determines the extent and direction of the behavioral phase change [101,102].

Phase sensitivity of resetting is best summarized by a phase-response curve (PRC), which plots the amplitude of phase change against the circadian phase when the phase shifting stimulus was provided. For instance,

the photic PRC is achieved by administering light pulses to free running animals at distinct time points across the circadian day (Figure 1a). The circadian day is defined as one activity-rest cycle, and by convention, the onset of activity is denoted as circadian time 12 (CT 12). Nocturnal animals exposed to a light pulse during the subjective day, known as the “dead zone”, experience no physiological change within the SCN or in wheel running activity in the subsequent days (Figure 1b). However, a light pulse in the early subjective night (CT 14) produces a phase delay in the onset of locomotor activity (Figure 1c), while a pulse at CT 18 results in a phase advance (Figure 1b). Interestingly, animals exposed to non-photic cues such as restricted availability of food and behavioral arousal, exhibit a similar but antiphasic PRC, with large phase advances occurring during the subjective day [103-105]. Surprisingly, chemogenetic activation of Drd1-SCN neurons mimics the behavioral phase shift to photic stimuli [40], suggesting that Drd1-expressing SCN neurons are able to influence photic sensitivity of the central circadian pacemaker.

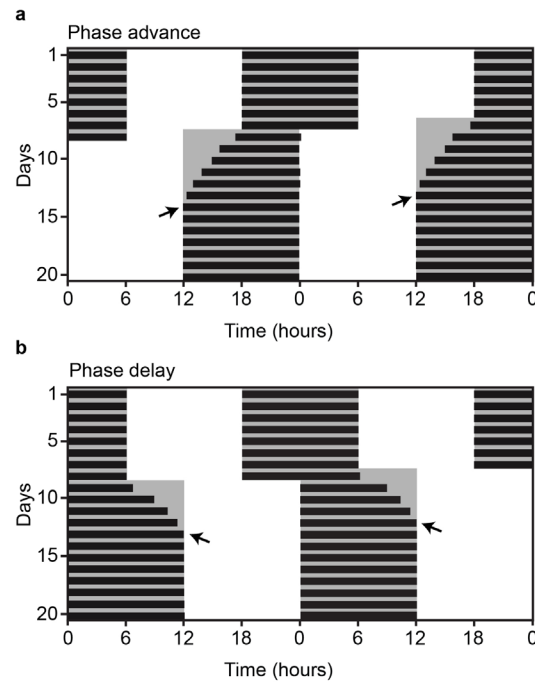


Figure 2. Jet-lag paradigms. Representative double-plotted actograms of an **a.** advance and **b.**, delay of the LD cycle by 6 hours. Black arrows indicate the day of entrainment.

An additional way to evaluate responsiveness to changes in environmental lighting conditions is through a shift in the LD cycle similar to what one would experience when jet-lagged. Transmeridian travel across several time zones creates a rapid change in environmental conditions leading to the general malaise and compromised daytime function associated with jet-lag disorder [3]. Jet-lag primarily is a consequence of imposed internal desynchrony within the SCN resulting from an incongruence between the phase of the endogenous circadian pacemaker and the local time. Reducing the duration of this desynchrony is a paramount concern for shift-workers who are constantly exposed to irregular work and sleep schedules, increasing their susceptibility to cardiovascular disease, ulcers, depression, and obesity [3,106]. As such, considerable effort has been placed into understanding the mechanism of circadian resynchronization in response to abrupt changes in environmental lighting conditions [40,107-109]. Jet-lag is simulated in the laboratory by advancing the LD cycle (Figure 2a: simulating eastward travel) or delaying it (Figure 2b: simulating westward travel). Resynchronization of wheel running activity to these shifts occurs gradually with incremental phase changes (transients) each day until a stable phase of entrainment has been achieved. Manipulations of the LD cycle paired with analysis of activity rhythms have been used to reveal the factors that influence the rate of entrainment. In

rodents, introduction of a novel running wheel, exposure to sexually receptive partners, or elevated DA tone have all resulted in accelerated circadian photoentrainment, demonstrating that arousal-inducing stimuli influence the rate of circadian resynchrony [40,110,111].

Most strikingly, *Drd1*-null mice exhibit a significantly diminished rate of photoentrainment to advances and delays of the LD cycle (Wild-type: ~ 6.5 days vs *Drd1*-KO: ~8.5 days) [40]. A normal photoentrainment rate is fully restored in these *Drd1*-null mice through viral-vector-mediated rescue of *Drd1* expression selectively within the SCN (SCN-Rescue: ~ 6.5 days; Figure 3a-c). Tracing studies suggest a direct connection from the VTA to the SCN, consistent with previous findings that electrolytic lesion of midbrain dopaminergic neurons results in a 40 percent reduction of DA levels within the SCN [40,112]. Chemogenetic activation of the VTA-DA neuron population is sufficient to accelerate the rate of photoentrainment in response to a 6-hour advance in the LD cycle [40]. From these recent discoveries, it is evident that *Drd1* signaling within the SCN remains functional through adulthood and that appropriately timed elevation of DA tone aids in the synchronization of endogenous rhythms to the environmental time cues. Because of the VTA's established role in reward, this direct neuronal connection could prove to be a major source of circadian rhythmicity disruptions associated with substance abuse,

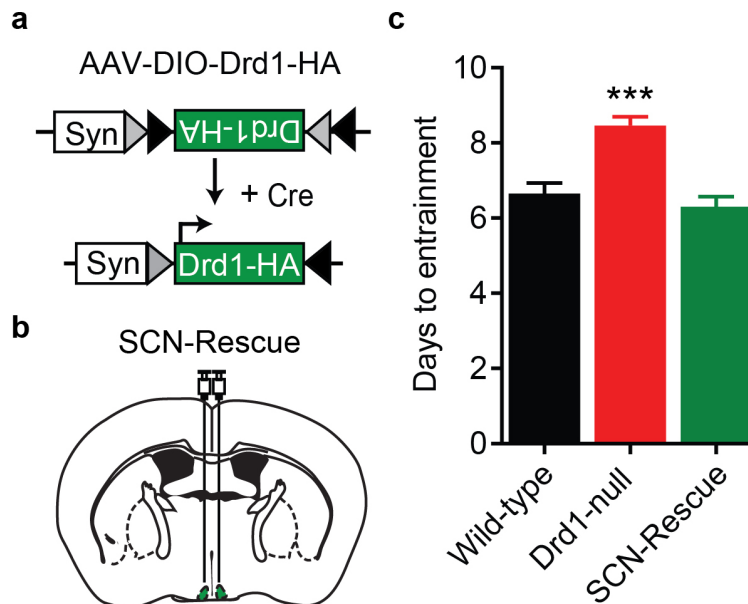


Figure 3. Drd1 expression in the SCN accelerates photoentrainment. **a.** Schematic representation of the Cre-dependent AAV-DIO-Drd1-HA construct used to re-express Drd1 expression within the SCN. **b.** Diagram of bilateral stereotaxic delivery of Drd1 re-expression virus to the SCN. **c.** Group analysis of days to entrain following a six-hour advance in the LD cycle; $F(2,62) = 19.42$; $P < 0.0001$; One-way ANOVA with Bonferroni post hoc comparison; $n = 13-26/\text{group}$; $***p < 0.0001$. Data are represented as mean \pm SEM. Reprinted from [40] with permission from Elsevier.

mood disorders, and neurodegenerative diseases. Further research based on these findings could provide the insight needed to develop effective therapeutic strategies to facilitate entrainment, thereby effectively treating disorders exacerbated by circadian desynchrony to environmental timing cues.

CONSEQUENCES OF ABERRANT ENTRAINMENT CONDITIONS

For humans, the advent of electricity and artificial lights has disrupted the sun's role in entraining circadian rhythms, resulting in serious health consequences including a range of metabolic disorders that have been detailed in the following review [113]. Even brief exposure to dim light at night can lead to significant weight gain and metabolic disruption [114]. Interestingly, a genetic mutation of the circadian core gene *Clock*, results in elevated DA signaling, dampened feeding rhythms, and metabolic disease in mice, suggesting an important role for circadian rhythms in energy regulation [115]. Along these lines, access to high-fat, palatable food also disrupts the timing of food intake and lengthens the period of free-running activity and temperature rhythms in mice [116,117]. This alteration of circadian timing suggests a connection between energy dense food intake and the circadian pacemaker. Recently, circadian peak of dopaminergic activity in and around the SCN has been found to be a

modulator of metabolism in rats [118]. Consequently, consumption of hypercaloric diets impairs adjustment to photic resetting and reduces light mediated *c-fos* mRNA induction within the SCN [119]. Additionally, regularly timed daily access to a palatable snack (chocolate pellet) entrains behavioral rhythms in constant darkness, reduces light-induced phase shifts, increases DA content in the forebrain, and increases *c-fos* mRNA expression within DA neurons of the midbrain [120]. These important findings uncover an underappreciated relationship between disrupted circadian rhythms and the dysregulation of the DA signaling. Future work must address how aberrant lighting conditions and rewarding foods impact the SCN, the consequence of this interaction, and how to reduce its negative impact.

CIRCADIAN DISRUPTION IN ADDICTION, MOOD DISORDERS, AND PARKINSON'S DISEASE

Based on the recent studies linking DA signaling to the circadian clock, and perturbations of circadian genes with drug addiction, it is critical to evaluate the connection between circadian rhythm disturbances and the abuse of addictive substances [121]. DA enhancing drugs such as cocaine or methamphetamine negatively impact circadian entrainment and sleep [122,123]. Cocaine abuse in pregnant females is particularly detrimental to the proper

function of the fetal SCN as exposure to cocaine during gestation results in prolonged disruption of photoentrainment after birth [124]. *Clock* mutant mice show overall hyperactivity, exaggerated locomotion in a novel environment, and high levels of sensitization to cocaine after repeated exposures [67]. These mice also exhibit a greater degree of place preference conditioning with low doses of cocaine, suggesting an elevated reward response to the drug. It is plausible that circadian genes directly regulate dopaminergic circuitry permitting circadian disruptions to alter the true value of a reward and the motivation for addictive substances [53,67,121,125,126].

In addition to drug addiction, several mood disorders and neurodegenerative diseases that involve alterations in DA neurotransmission are accompanied by increased disruptions in circadian rhythms [32,127]. Major depressive disorder (MDD) is commonly associated with sleep abnormalities and a reduction in the amplitude of daily oscillations of body temperature, cortisol, and melatonin rhythms [128]. Bipolar disorder (BD), is characterized by alternating episodes of mania and depression which result in significant sleep and circadian disruptions. Elevated DA contributes to manic episodes in BD and may be a factor in the entrainment disruption. Circadian disorganization is also observed in Parkinson's disease (PD), a neurodegenerative disorder where loss of nigrostriatal dopaminergic neurons results in tremors, impaired balance, depression, and deterioration of the sleep-wake cycle [74,75,129]. PD patients demonstrate a reduction in nighttime sleep quality, alertness, and cognitive performance which can all be attributed to alterations in circadian entrainment [74]. In a mouse model of PD, in which progressive degeneration of midbrain DA neurons is chemically induced, rest/activity patterns show a gradual decline in amplitude and stability [130]. Further evaluation of how neurodegeneration of dopaminergic neurons influences circadian rhythms may provide novel diagnostic tools to detect PD earlier in its progression than currently possible. Additionally, improving the circadian rhythmicity of high-risk patients (*i.e.* through regulation of lighting conditions and feeding times), may help to alleviate negative consequences of sleep disturbances and inappropriately timed bouts of wakefulness associated with the disease.

In general, circadian disruption is known to occur during the natural aging process. The elderly are susceptible to reduced amplitude in rest-activity cycles, body temperature, hormone levels, SCN firing rate, and they experience fragmented patterns of sleep [131]. Chronobiological treatments in the elderly, using light and physical exercise have shown promising benefits which boost the circadian rhythm amplitude when provided during the correct phase of the circadian cycle [132]. Further elucidation of the reciprocal relationship between aberrant

DA signaling and circadian disruptions may aid in the development of novel chronotherapeutic strategies for psychiatric or some neurodegenerative disorders.

CONCLUSIONS AND OUTLOOK

Circadian rhythms perform a vital role in orchestrating all aspects of physiology to ensure that rest and active states are properly aligned with the solar day. However, obligatory schedules of modern society disrupt natural oscillations of biological clocks. Disturbing these rhythms increases the likelihood of metabolic, mental and physical disorders, thereby increasing the burden on healthcare around the globe. A challenge for researchers and clinicians is to elucidate the precise mechanisms of circadian rhythm disruptions and how to reduce their negative impact on well-being.

While significant advances have been made in the field of circadian biology, pressing issues remain. For instance, the processing of light information from the retina to the SCN has been well characterized, however, the mechanism of how the SCN communicates with the rest of the brain and body is less understood as reviewed in [133]. A mechanistic understanding of how the SCN integrates and relays photic and non-photoc information to generate high amplitude biological rhythms is necessary to understand how daily physiological and metabolic rhythms deteriorate under certain conditions [134]. Furthermore, it is still unclear whether restoring the SCN oscillation amplitude would be enough to alleviate pathologies associated with circadian misalignment. In addition, maladaptive changes in the dopaminergic system underlie many neurological diseases such as depression, bipolar disease, and Parkinson's disease, which share symptoms of circadian and sleep disruption. Thus, a mechanistic understanding of how dopamine signaling coordinates with the circadian system to govern daily physiological and behavioral functions will provide novel therapeutic avenues for these disorders. The integration of information learned from translational animal experiments into human clinical studies will be the next critical step toward identifying treatment plans to effectively alleviate symptoms of circadian rhythm disorders.

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