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A Complex Relationship Among the Circadian Rhythm, Reward Circuit and Substance Use Disorder (SUD)

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Abstract: The human brain not only controls the various physiological functions but is also the prime regulator of circadian rhythms, rewards, and behaviors. Environmental factors, professional stress, and social disintegration are regarded as the initial causative factors of addiction behavior. Shift work, artificial light exposure at night, and chronic and acute jet lag influence circadian rhythm dysfunction. The result is impaired neurotransmitter release, dysfunction of neural circuits, endocrine disturbance, and metabolic disorder, leading to advancement in substance use disorder. There is a bidirectional relationship between chronodisruption and addiction behavior. Circadian rhythm dysfunction, neuroadaptation in the reward circuits, and alteration in clock gene expression in the mesolimbic areas influence substance use disorder (SUD), and chronotherapy has potential benefits in the treatment strategies. This review explores the relationship among the circadian rhythm dysfunction, reward circuit, and SUD. The impact of chronotherapy on SUD has also been discussed.

Keywords: SCN, circadian rhythm dysfunction, melatonin, cortisol, drug addiction

Introduction

Circadian rhythms are the rhythmic appearance of physiological functions, happening over a period of 24 hours. These rhythms are controlled by the hypothalamic suprachiasmatic nucleus (SCN), which is considered the biological clock. Circadian rhythms are endogenously generated and synchronized with the environmental light/dark (LD) cycle. Several factors regulate circadian rhythm. These factors are called zeitgebers (time cues/time givers). LD cycle, environmental temperature, feeding pattern, and social interaction are the external or environmental zeitgebers, while sleep-wake cycle, melatonin secretion, and metabolic process are the internal zeitgebers. Jet lag, shift work, and artificial light exposure at night disrupt the circadian rhythm, leading to problems in the sleep-wake cycle and cortisol secretion, melatonin rhythm, metabolic activities, and expression of different clock control genes in the mesolimbic areas.

The neurons of SCN rhythmically express clock control genes that are under a transcriptional regulation system. Expression of clock genes occurs in many regions of the brain and peripheral tissues that are synchronized with SCN. SCN transmits the signal to the different brain regions and the pineal gland, which secretes melatonin.[1] Addiction to alcohol and other substances (cannabis, psychostimulants, and opioids) is a major issue throughout the world and is also

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associated with global public health concerns. Drug addiction affects individuals' health and well-being and creates problems in families and communities. Several evidences suggest a bidirectional connection between circadian rhythm dysfunction and substance abuse. Circadian rhythm dysfunction promotes substance use disorders (SUDs) and shows greater dependence on illicit and licit drugs.[2] Chronodisruption has been observed in individuals having addictive disorders.[3,4] Fundamentally, chronodisruption is associated with circadian rhythm misalignment. It refers to the disturbance or alteration of normal rhythms of physiological functions in association with alteration in LD cycle, jet lag, and social activities. Patients with alcohol addiction exhibit many symptoms of circadian dysfunction. Drug abuse stimulates glutamatergic and dopaminergic pathways in the SCN and the subcortical areas, leading to alteration in clock gene expression and advancement in drug addiction. Alcohol intake in adult animals (rats) and perinatal stage can alter free running period and photic responsiveness in the SCN. Application of brief light pulse during early or late night had no effect on circadian pacemaker in rats those were habituated to chronic ethanol intake.[5] Several authors studied the relationship between SUD and circadian rhythmicity on human subjects. A study on 41 men (age 16 years or less), taking multiple substances showed neuropsychological problems. Early onset of substance use exerts severe complications like low IQ (intelligence quotient) levels, higher visuoperceptual and planning deficit. Consumption of substances may affect neurodevelopment.[6] Circadian rhythmicity in SUD, schizophrenia with SUD, and schizophrenia patients was studied. A total of 165 male patients were divided into three groups (55 patients in each group): schizophrenia, schizophrenia with SUD, and SUD. The control group carried 90 healthy individuals. Longer sleeping time (delayed awakening) was observed in schizophrenia and schizophrenia with SUD patients. SUD patients showed less sleeping hours and morning typology. Patients with schizophrenia and SUD exhibit a distinct pattern of distal skin temperature and impaired wakefulness.[7] Antúnez et al studied the effect of circadian rhythmicity in 40 male SUD patients and 40 SUD with major depressive disorder (MDD) patients. Alteration of circadian rhythm occurs in both SUD and SUD with MDD subjects. Patients showed morningness during ambulatory and therapeutic community treatment.[8]

Mesocorticolimbic circuits act as the brain reward system. The ventral tegmental area of the midbrain, nucleus accumbens, amygdala, hippocampus, and medial prefrontal cortex are the parts of the reward circuit, which is operated by dopaminergic signals. Pierce and Kumaresan reported that this circuit is stimulated at the initial time of reward phase after drug intake. Repeated drug use causes neuroadaptation in the reward circuits and promotes inductive effects.[9] The pharmacological and motivational effects of drugs increase drug seeking, drug intake, and drug tolerance, and finally complete the drug use and abuse cycle.[10] The current review has highlighted the relationship among the circadian rhythm dysfunction, reward circuit, and SUD. More specifically, the relationship between clock gene expression and SUD has given emphasis. The impact of chronotherapy on SUD has also been considered for therapeutic strategies.

Circadian Rhythm

The endogenous physiological events oscillate around the clock along with environmental factors (light-dark cycle, temperature); these rhythmic oscillations of the physiological phenomenon are called circadian (*circa* = about; *dies* = day) rhythm. The SCN of the hypothalamus performs as the circadian clock that is synchronized with the environmental light–dark cycle. The retinohypothalamic tract (RHT) from intrinsically photoreceptive retinal ganglion cells (ipRGCs) of the retina transmits photic signal to the SCN. These particular cells express melanopsin for perception of blue light (~480 nm).[11,12] RHT is the glutamatergic pathway that activates the Ca^{2+}-mediated intracellular signaling cascade in the SCN. At the molecular level, a transcriptional–translational feedback loop (TTFL) operates the circadian clock in the SCN. Circadian locomotor output cycle kaput (CLOCK), and brain and muscle ARNT-like protein 1 (BMAL1) form a heterodimeric (CLOCK:BMAL1) complex that interacts with E-boxes and induces the transcription of *Period* (*Per1, Per2*, and *Per3*) and *Cryptochrome* (*Cry1* and *Cry 2*) genes. Later, PER and CRY proteins make heterodimer in the cytoplasm and moves into the nucleus, where they repress CLOCK:BMAL1 complex-induced transcriptional activity. CLOCK:BMAL1-mediated transcriptional activation occurs in the early morning, whereas PER and CRY protein-dependent repression starts in the evening/night.[13] Other two factors REV-ERB α and RORα competitively bind with the retinoic acid-related orphan receptor (ROR) response elements in the *Bmal1* promoter.[14] REV-ERB α increases the expression of *Bmal1*, but RORα inhibits the expression. Unusual light exposure dysfunctions the activity of circadian clock, which disturbs many physiological rhythms, including sleep-wake cycle, cortisol, and melatonin

secretion.[15] Exposure to artificial light at night during shift work, night work, and jet lag causes alteration in the expression of core clock genes. The SCN also controls melatonin release from the pineal gland. Additionally, glucocorticoid secretion shows a circadian rhythm under the influence of the hypothalamic-pituitary-adrenal (HPA) axis. Disruption of circadian rhythm alters cortisol and melatonin levels in the blood (higher concentrations of cortisol and lower values of melatonin).[16]

Glutamate is an excitatory neurotransmitter in the CNS. The RHT is also a glutamatergic projection. This neurotransmitter increases neuroplasticity and drug-seeking behavior after a withdrawal effect. Glutamatergic neural circuits are present among the prefrontal cortex (PFC), amygdala, nucleus accumbens (NAc), and ventral tegmental area (VTA) that promote drug craving during withdrawal.[17] The expression glutamate transporters are under the control of clock genes that are regulated by SCN-mediated photic signaling.[18] The SCN output also regulates the functions of the paraventricular nucleus (PVN) in the hypothalamus. The PVN controls melatonin and cortisol rhythm. The PVN is associated with stress-induced alcohol or drug addiction.[19] Abstinence of substance abuse causes reward deficiency syndrome and promotes drug seeking. A survey report indicated that inherently weak cortisol rhythm in adolescents exacerbated alcoholism.[20]

GABAergic neurotransmission is one of the regulatory mechanisms in the SCN. Although glutamate is the major excitatory neurotransmission in the SCN, co-lateral GABAergic connections regulate the SCN functions. GABA acts through GABA-A and GABA-B receptors. The Activity of GABA-A receptors is associated with alcoholic behaviors. Quantitative trait locus (QTL) studies in mice model systems revealed that alcohol drinking affects GABA-A genes along with the expression of glutamate decarboxylase, resulting in a disturbance in the regulatory system.[21]

Circadian Rhythm Disruption, Sleep Problem and Addiction Behavior

Chronodisruption contributes to addictive disorders and dependency. Drug addiction is a serious problem for global public health. Addiction behavior has an effect on individuals' health and creates disturbances in families and communities. Circadian rhythm has a bidirectional relationship with drug addiction, including alcohol, cannabis, hallucinogens, psychostimulants, and opioids.[22,23] Alteration of clock gene expression in different areas of the brain, primarily in subcortical areas occurs during the initial stage of drug addiction that promotes drug reward and drug-seeking activity (Figure 1). It is assumed that glutamatergic and dopaminergic pathways may create a link between circadian rhythm and drug addiction.[22,23]

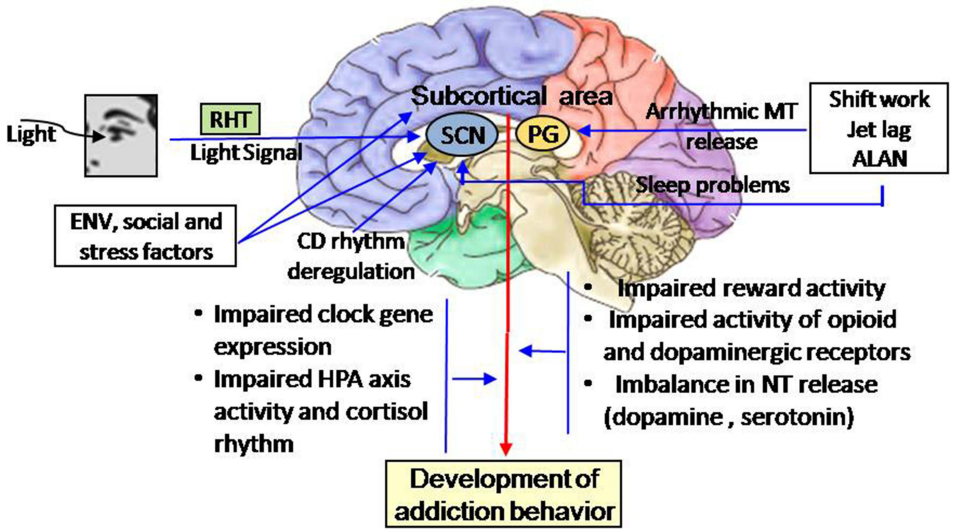

Figure 1 The relationship among the circadian rhythm dysfunction, reward circuit, and substance use disorder (SUD).
Abbreviations: ALAN, Artificial light at night; CD, Circadian; ENV, Environmental; HPA, Hypothalamic-pituitary adrenal axis; MT, Melatonin; NT, Neurotransmitters; PG, Pineal gland; RHT, Retinohypothalamic tract; SCN, Suprachiasmatic nucleus.

Circadian rhythm disruption happens during shift work, night work, jet lag, and exposure of light-at-night.[24] The SCN acts as a central clock in the circadian system. The SCN receives photic signal from the retinal ganglion cells in connection with the RHT. The SCN also transmits the efferent signals to the hypothalamus, brainstem, pituitary gland, pineal gland, and other areas of the brain. The SCN synchronizes the activity of peripheral clock. Thus, the SCN regulates the activities of different organs. Artificial light exposure at night during shift work, night work, or other activities cause phase shifting and changes the expression of core clock genes. The SCN controls the pineal melatonin secretion, which occurs at night.[25] Exposure to light at night decreases melatonin secretion, which turns the cells from night mode to day-mode (active). This alteration deregulates gene expression, metabolic activities, and other protective functions. The HPA axis regulates glucocorticoid secretion. The SCN regulates the function of HPA axis and maintain the rhythmic secretion of glucocorticoid. Circadian rhythm disruption changes secretion pattern of glucocorticoid release. Thus, circadian dysfunction deregulates the neuroendocrine functions and metabolic activities.[26] Chronodisruption promotes neuropsychiatric disorders,[26,27] which increases the risk of drug abuse.[4] Gulick and Gamsby reported that shift workers and adolescents were prone to circadian rhythm disruption and susceptible to addiction.[19] Women who have little social support and a past history of substance abuse or affective disorders are vulnerable to alcohol addiction or substance abuse disorder.[28] Circadian rhythm disorder intensifies sleep disorders, and the reverse is also true. The American Academy of Sleep Medicine classified the circadian rhythm sleep disorders (CRSDs) into four categories: (i) advanced sleep phase disorder/syndrome (ASPD/ASPS), (ii) delayed sleep phase disorder/syndrome (DSPD/DSPS), (iii) free running disorder (FRD), (iv) and irregular sleep-wake rhythm/pattern (ISWR).[29] ASPD is characterized by early sleep onset and advanced awakening than the desired time. DSPD exhibits delayed onset of sleep and awakening. Irregular sleep-wake cycle (1–2 hour/s progressive delay) occurs in FRD. The variable episodes of sleeping and waking behavior appear in ISWR. Sleep disorders advances alcohol and substance abuse behaviour. Alternatively, substance abuse induces sleep disorders. Cocaine and amphetamine cause restlessness and sleep deprivation. Benzodiazepines, alcohol, and heroin enhance daytime sleepiness and reduce sleep latency at the early stage but increase night awakening at the later phase.[2] There is a bidirectional relationship between substance abuse and sleep disorders.[2] Sleep disturbance affects the reward circuit and influences alcohol use.[30] Older adults some times addicted to alcohol and drug to compensate against circadian rhythm sleep disorders.[31] Some prescribed drugs can increase the risk of drug addiction. For example, benzodiazepines are prescribed to old age people to reduce anxiety and sleep problems, which are highly addictive.[32]

Phenobarbital can promote phase-advance in rats. Nicotine promotes phase advance of sleep rhythm (earlier wake) while alcohol shows phase delay in sleep pattern.[19] Drug addiction disrupts the pattern of REM sleep[33] that advances mood disorders, cognitive deficits, and behavioral problems. Withdrawal or abstinence from drugs creates stress with sleep issues. Alcohol consumption suppresses melatonin release in humans, leading to sleep deprivation.[34] Deregulation of melatonin rhythm is dose-dependent. Higher dose increases the time span for the melatonin output.[2] Application of melatonin or its pharmacological analogs helps in the resynchronization of oscillation between SCN and peripheral clocks to prevent relapse-like behavior.[35,36]

Circadian Disruption, Clock Gene Expression and Drug Addiction

Drug abuse has negative effect on circadian system.[37] Circadian dysregulation causes alteration of core clock gene expression in the different areas of the brain (Table 1). Drug abuse alters the expression of *Per1* and *Per2* genes in the hippocampus, VTA, and NAc in rat model systems.[38] Ozburn et al reported that chronic alcohol abuse diminished *Clock* gene expression in the NAc and VTA.[39] Drug addiction and alcoholism also causes circadian dysfunction, resulting in sleep problems, impaired eating habits, and body temperature regulation.[19] Brower et al reported that a polymorphism in the *Per3* gene induces sleep disturbances in alcohol use disorder (AUD).[40] Chronotype is another factor for drug use. Evening circadian typology increases the risk of excess drug consumption, while morning typology can be protective against drug use.[37] Polymorphisms are associated with chronotype. Polymorphisms in *Per3* and *Clock* can influence evening chronotype,[40,41] while polymorphisms in *Per1, Per2*, and *Per3* exhibit morningness.[22,42] People with an evening chronotype are facing problems with sleep disorders, psychiatric problems, and addiction behavior.[37,43] This chronotype

Table 1 A List of Circadian Clock Genes of Human, Their Functions and Impact on SUD

Genes	Protein	Functions	Altered Expression Circadian Clock Genes in SUD
Per1	PER 1/2/3 (PER - Period)	PER protein represses CLOCK-BMAL1-mediated transcription activation	Altered expression of *Per1* and *Per2* genes in the hippocampus, VTA, and NAc occurs during drug abuse Polymorphisms of *Per* genes cause AUD Cocaine suppresses *Per* gene expression in the SCN and NAc
Per2			
Per3			
Cry1	CRY 1/2 (CRY - Cryptochrome)	CRY and PER forms heterodimer and represses CLOCK-BMAL1-mediated transcription activation	Arrhythmic expression of *Cry* genes occurs in the SCN and NAc during cocaine addiction
Cry2			
Clock	CLOCK (Circadian locomotor output cycles kaput)	CLOCK and BMAL1 form heterodimer to increase the expression of target gene (*Per* and *Cry*)	Alcohol abuse decreases *Clock* gene expression in the VTA, and NAc Polymorphisms of *Clock* gene increases alcohol consumption Cannabis decreases *Clock* gene expression *Clock* mutation promotes cocaine addiction
Bmal1	BMAL1 (Brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1)	BMAL1 interacts with CLOCK and induces ine expression of various clock components.	*Bmal1* expression decreases during AUD Cocaine increases *Bmal1* expression in the hippocampus and PFC
Arntl2	ARNTL2 (Aryl hydrocarbon receptor nuclear translocator like)	Its activity is similar to BMAL1	Cannabis increases the expression of the *Arntl*
CK1ε	CK1ε (Casein kinase 1 epsilon)	CK1ε/δ phosphorylates PER protein and promotes its degradation	Inhibition of casein kinases prevents alcohol relapse
CK1δ	CK1δ (Casein kinase 1 delta)		
Rev-Erbα	Reverse-erythroblastosis α	REV-ERBα increases the expression of *Bmal1*	Methamphetamine alters *Rev-erbα* expression in the striatum

is very common in adolescents and also causes social jet lag. Wittmann et al reported that individuals with evening chronotype consumed excess amounts of alcohol.[44]

Drug withdrawal is also associated with chronodisruption. Animal experiments showed that opiate withdrawal hampers circadian rhythm, hormone release, and core clock gene expression in the SCN, VTA, PFC, amygdala, NAc, striatum, and hippocampus[45,46] Li et al reported that heroin withdrawal deregulated the expression of the *per1* and *per2* genes in human peripheral blood mononuclear cells.[47] There was also evidence of arrhythmic hormone release.

Alcohol Addiction

Alcohol abuse impacts on rhythmic activity of the circadian system.[48] Common symptoms of AUD are sleep disorders, impaired core body temperature, and deregulated cortisol and melatonin rhythm.[16] Alcohol abuse decreases arginine vasopressin (AVP), vasoactive intestinal polypeptide (VIP), gastrin-releasing peptide (GRP), and somatostatin (SST) expressing neurons in the rat SCN.[49] Both AVP and VIP-expressing neurons are differentially present in the ventral and dorsal part of the SCN.[50] Reduction of AVP and VIP neurons in the SCN advances the risk of alcohol drinking.[51]

Several authors showed the alteration in clock gene expression in various cells. Human peripheral mononuclear cells of AUD patients decrease *Clock* RNA expression.[52] McCarthy et al reported that fibroblast cells from AUD patients showed irregular expression of the *Per2* gene.[53] Mutation in the *Per2* gene increases glutamatergic signaling, leading to alcohol addiction.[54] Polymorphisms in the *Per* genes influence alcohol addiction. Knockout or mutation of the *Per* genes

in the experimental animals showed addiction behavior.[55,56] *Per2* mutation causes severe alcohol affection behavior. *Per2*$^{-/-}$ mice consume excessive amounts of alcohol and show alcohol-seeking behaviors.[57] *Per2* mutation causes hyperglutamatergic and hyperexcitability, leading to more alcohol consumption.[54] Acamprosate, a pharmaceutical agent that prevents hyperglutamatergic conditions, is used for the treatment of patients with alcohol addiction.[58] Treatment with acamprosate decreases alcohol drinking.[59] Inhibition of casein kinase 1 (CK1ε/δ) prevents alcohol relapse.[60] Clock genes are not only expressed in the SCN but also expressed in different areas of the brain, including mesocorticolimbic area. Mutation in *Per1, Per2, Clock*, and *Arntl* genes causes circadian disruption, alteration in dopaminergic and glutamatergic activity, reward circuit, and behavioral activity, resulting in alcohol craving.[54,61–63]

The *Clock* gene is also associated with alcohol addiction. Sjoholm et al reported that a particular haplotype of *Clock* single nucleotide polymorphisms (SNPs) showed a greater risk of depression and alcoholism.[61] *Clock*Δ19 mice are hyperactive and prefer more alcohol to consume.[39] Ando et al and Huang et al indicated that *Bmal1* expression decreased in alcohol drinkers.[52,64] Reduction of *Bmal1* expression decreases CLOCK:BMAL complexes-mediated transcriptional machinery, leading to alcohol-seeking and withdrawal behaviors.

The effects of alcohol and other drugs affect circadian rhythmicity via the dopaminergic system, which is linked with the reward pathway and circadian system. Wolstenholme et al studied ethanol intake in C57BL/6J (high alcohol preferring) and DBA/2J (alcohol non-preferring) adolescent mice using drinking in the dark (DID) model. In low dose drinking, total alcohol consumption was same in both types of mice. However, ethanol consumption in early adolescent in C57BL/6J mice showed increased ethanol intake in adult life.[65] This may be linked with dopamine receptor expression. Complete expression of dopamine receptors occurs during adolescent. Dwyer and Leslie reported that expression and maturation of D1R and D2R mostly happened in adolescent rodents that may be associated with addiction behaviour.[66] D1R controls the expression of core clock genes.[67] The projection from VTA to the SCN is D1R dependent and impacts circadian rhythm.[68] Antagonist of D1R and n-methyl-d-aspartate (NMDA) receptor inhibits the addictive effects of methamphetamine and circadian dysfunction.[69] Additionally, D2R drives *Per2* expression in the VTA of the reward circuit.[70]

Shift workers show greater alcohol susceptibility.[19] Similarly, social jet lag influences alcohol addiction in adolescents and adults.[19] Circadian desynchrony affects the functions of the PFC, which appears in the growing phase during adolescence period. Girls show earlier connectivity of PFC than boys. This indicates the sex dependency of the early phase of alcoholism.[19] Constant light exposure to the experimental animals showed alcohol affection.[71] Therefore, circadian misalignment changes the expression pattern of core clock genes, affects the activity of the reward circuit, and changes the levels of neurotransmitters (glutamate, dopamine, serotonin, GABA) that collectively advance addiction behavior.

Cannabinoids Addiction

Cannabinoids (marijuana addiction) are the psychoactive agents. They act through cannabinoid receptors type 1 (CB1) and type 2 (CB2). CB1 receptors are expressed in the brain. CB1 receptors appeared in the late afternoon and evening, which increased drug use.[72] There is an association between cannabinoids, circadian rhythms, and the endocannabinoid (endogenous receptors and ligands) system.[73] The endocannabinoid system regulates sleep, hunger, body temperature, cognition, circadian rhythm, and activity of microglial cells.[23] Cannabinoids affect the function of the SCN. Cannabis increases the expression of the *Arntl* gene and downregulates *Clock* gene output.[73] Delta-9-tetrahydrocannabinol (THC), a bioactive component of cannabis alters circadian rhythm and sleep physiology- low sleep latency, daytime sleepiness, and easy-to-go asleep.[74]

Serotonin is one of the neurotransmitters in CNS and is also involved in raphe nucleus-SCN projection. There are seven classes and different subclasses of serotonergic receptors. In rodents, 5HT1A receptors act during their active phase (at night), and 5HT2A receptors exhibit activity during the daytime (light period).[75] Psychedelic drugs act through the serotonergic receptors. 5HT2A and 5HT2C receptor agonists decreased melatonin output and showed a reverse effect in case of antagonist use, indicating the role of serotonin response on the SCN-pineal axis.[76] β-carbolines, a psychedelic component increases the stability of PER2 protein and prolongs the circadian period.[77]

Psychostimulant

Amphetamines, methylxanthines, and cocaine are the psychostimulant drugs. They are the stimulant of the mesolimbic dopaminergic system for controlling reward, motivation, and cognition. Cocaine is considered a chronodisruptive agent. Cocaine affects the circadian system, while the circadian system modulates cocaine intake.[78] Experimental studies revealed that cocaine treatment affected SCN functions. Cocaine alters the rhythmic expression of *Clock, Bmal1, Cry1* and *Per* genes in the SCN.[79] *Clock* mutant mice (*Clock*Δ19 mice) showed increased cocaine conditioned place preference (CPP) than non-mutant.[80] Moreover, *Clock*Δ19 mutants had a high level of dopaminergic signal in the VTA and also increased the glutamatergic signal, leading to uplifted addiction behaviors.[78,81] Wang et al reported that in rats, cocaine suppresses the expression of *Per2, Per3*, and *Cry* in the SCN and *Per3, Cry, Bmal1* and *Clock* in the NAc.[4] On the other hand, it stimulates the expression of *Per1, Per2, Cry1*, and *Bmal1* in the hippocampus and *Per1, Per2, Per3*, and *Bmal1* in the PFC.[4] Thus, cocaine disrupts the expression of core clock genes in the SCN and in the reward-related circuits of mesocorticolimbic areas of the brain. The experimental result revealed that the expression of clock genes occurred differentially in the different areas of the brain that were associated with mood and reward circuits. Upregulation of *Per1* and *Per2* expression and downregulation of *Bmal1* and *Cry1* expression occurred in the hippocampus, while upregulation of *Per1* and *Clock* expression appeared in the caudate and putamen.[82] Lynch et al reported that the *Per2, Cry1, Bmal1*, and *Clock gene* expression increased in the dorsal striatum.[83] In NAc, *Npas2, Per1*, and *Per3* expression were upregulated.[79] Thus, CLOCK and NPAS2 regulate the function of reward-related areas after cocaine administration. *Per1 and Per2* mutant mice showed different results for cocaine CPP. *Per1* mutant mice did not have a major response in CPP, while *Per2* mutant showed a significant response in CPP.[84] Moreover, cocaine modulates the serotonergic signaling in the SCN.[85] Cocaine disrupts corticosterone and prolactin rhythms in rats.[86] Cocaine-induced alteration in core clock gene expression in the various brain regions changes the circadian pattern, reward, behavior, and cocaine affection. *Per* and *Clock* genes increase cocaine craving and cocaine-mediated reward in mice.[23] In humans, polymorphism of the *PER2* gene is associated with cocaine abuse.[87]

Methamphetamine alters the dopaminergic signal in the substantia nigra and striatum of basal ganglia.[88] In mice, dopaminergic and glutamatergic signaling alters *Per1* and *Per2* expression in the SCN and *Per1, Per2, Bmal1*, and *Rev-erbα* expression in the striatum after injection of methamphetamine.[89] Methamphetamine modulates serotonergic signals in the SCN.[90,91] Methylphenidate alters the expression of the clock gene in the SCN.[92] Amphetamine changes the expression of the *Per1, Per2*, and *Rev-erbα* genes in the rat striatum.[93] Thus, not all psychostimulant drugs act on the SCN but alter the activity of different circuits in the subcortical areas that collectively affect circadian rhythm and behavior.

Opioids

Opioids are the alkaloids of the opium poppy plant (*Papaver somniferum L.*) (natural), heroin (semi-synthetic), fentanyl, and methadone (synthetic). Opioids act through the opioid receptors, which regulate motivation, reward, mood, depression, and stress. Continuous light exposure increases morphine intake in rat and increase the expression of *Per1* and *Per2* in the striatum,[94] indicating the imbalance in the circadian rhythm. Opiate exposure downregulates *Per2* expression in the SCN and imposes phase advance circo-locomotive activity.[95,96] Animal experiments showed excess heroin craving during the dark phase than the light phase.[97] Liu et al reported that morphine decreased *Per1* expression, as well as extracellular signal-regulated kinase (ERK) activity.[98] *Per2* mutant mice showed low tolerance to morphine.[99] Morphine modulates the activity of the forebrain, including SCN, and alters motivation, behaviors, and circadian patterns. Heroin disrupts cortisol rhythm in humans.[47] Morphine also disrupts ACTH and melatonin rhythm.[45] Moreover, Li et al also reported that opiate use and its withdrawal alter the expression of clock genes in the SCN and other areas of the brain (amygdala, hippocampus, NAc, PFC, and VTA) that were involved in the controlling of circadian rhythm and reward function.[45] Thus, opioid addiction disturbs the circadian rhythm, which can progress addiction behavior in later stages.

Reward Circuit, Neurotransmission, and Addiction Behavior

Drugs, associated with addiction effects have differential activity on the central nervous system (CNS). The abuse of drugs starts with a recreational response. Repeated use of the drugs increases gratifying effects that make a positive reinforcement. The initial enjoyable effects are mediated by the brain reward system, which is under the dopaminergic mesocorticolimbic circuits, comprised of the VTA of the midbrain, NAc, amygdala, hippocampus, and medial prefrontal cortex (mPFC).[9] Repeated use of drugs causes neuroadaptations in the reward circuits, leading to inducible effects. Later, persistent and long-term plasticity in the reward circuits influences the addiction effect,[100] and drug abuse converts into compulsive use from impulsive use. This compulsive drug use provides relief from stress and anxiety and also alleviates some physical or psychological stress.[101] Withdrawal of drugs decreases the activity of the reward circuit[102] and increases brain stress that activates the HPA axis. Hypothalamic corticotrophin release factor (CRF) increases the secretion of cortisol from the adrenal cortex via the HPA axis. Excess cortisol alters physiological activities.[103] Finally, drug addiction emerges as a drug-craving behavior in which multiple brain regions are associated. Dysfunction in the regulatory process of the PFC, retrieval of emotional memories in the basolateral amygdala, and activation of the hippocampus, orbitofrontal cortex, anterior cingulate, dorsal striatum, and insula promote the compulsive desire for drugs. Glutamate from the PFC and the basolateral amygdala operates this circuit.[101]

One area of importance has to do with the term "Reward Deficiency Syndrome (RDS). RDS is a psychological theory first noted by Kenneth Blum in 1995.[104] It is characterized by reward-seeking behavior and/or addictions. RDS commonly characterized by breakdown of neurotransmission, which promotes a wide range of addiction, compulsive, and, impulsive behaviour.[105,106] Studying from genetic variations, it is assumed that those carrying the D2A1 allele as well as many other reward gene polymorphisms are susceptible to RDS. Importantly, people having the A1 allele showed less numbers of D2 receptors in their brain, leading to poor pleasure and reward feelings from activities, which would give pleasure to the others.[107] The result is addiction, mood disorders, compulsions, impulsivity, and other spectrum disorders. These individuals showed low levels of dopamine, and they do not feel sufficient pleasure from normal activities. This increases their interest towards addictive drugs or behaviors like gambling. The premise that "all roads lead to dopamine"[108] is still essential for therapeutic purpose, and it can prevent relapse and possibly eliminate many RDS behaviors. Future research will undoubtedly clarify the role of genetic polymorphisms and associated behavioral endophenotypes.[109]

A person who is suffering from reward deficiency may feel the same degree of pleasure as normal individuals after getting the addictive stimuli. This addictive stimulation changes the activity of the reward center of the brain as well as neurotransmission. Certainly, there is strong evidence from genome wide association studies (GWAS) to implicate not only the DRD2 A1 allele but other reward gene polymorphisms as well.[110,111] Drug addiction or addictive behavior can initiate genetic abnormalities of D2 receptor. Moreover, genetic abnormalities as well as reward deficiency in an individual influence to seek addictive substances and behaviours. Most interestingly, circadian rhythm is one additional causative issue especially as it relates to SUD.[112] Genetic study indicated that polymorphic dysfunction of a number of reward genes, including dopamine D2 (-DRD2/ANKK (Taq1A)), OPRM1 (A/G), DRD3 (C/T), and MAOA (4R) are also involved.[113]

Chronodisruption alters the activity of the circuit of reward function that influences drug addiction. Dopaminergic neurotransmission is associated with drug-induced reward and is also involved in biological rhythms.[114] Dopamine-induced activities maintain locomotor activity, core body temperature, and secretion of glucocorticoid. Normally, dopamine synthesis, release, and transmission in the CNS maintain a circadian pattern. Moreover, the expression of dopamine receptors (D1R and D2R) occurs in circadian fashion.[115] Thus, the circadian rhythm of dopaminergic activity is associated with normal circadian activity as well as rewarding effects.[3] There is a link between SCN and dopaminergic activity. VTA and substantia nigra provide a huge amount of dopamine in CNS. Moreover, VTA expresses the core clock genes.[115] Tyrosine hydroxylase (TH) and monoamine oxidase (MAO) maintain the dopamine levels in VTA and striatal area. D1R, D2R, and D3R control the activity of dopamine. NPAS2, CLOCK, and BMAL1 have a regulation on the activity of D3R (Giα-mediated response) and MAO because their promoter contains an E-box. CLOCK negatively and NPAS2 positively regulate the expression of MAO and D3R, respectively.[49] *Clock* mutation dampens the expression of

GABAergic genes in the VTA, resulting in withdrawal of GABAergic response. This disinhibitory activity increases dopamine release and affects the addiction behavior.[78] These activities deregulate the circadian activity of dopaminergic signaling. The SCN also sends signals to the VTA via the medial preoptic nucleus of the hypothalamus for the regulation of reward-related behavior.[116] Mendoza and Challet reported that the down-regulation of clock gene activity affects dopamine-related activity like drug addiction and psychological disorders.[117]

It is well-known that photoperiod affects dopaminergic activity.[118] Neuroscience researchers worldwide have been working hard to comprehend and characterize the role of neurotransmission in mesolimbic brain regions and the prefrontal cortex. Our group presented proof in the 1970s that rats subjected to darkness significantly increased their alcohol consumption.[118] We suggested that melatonin was to blame at that time because pineal activity enhances ethanol preference.[119] In addition, our laboratory, along with a few others, postulated that dopamine-acetaldehyde adducts increase alcohol consumption in both rodents and humans. Although research in these areas has significantly decreased over time, more current scientifically substantiated studies continue to highlight the significance of these earlier contentious hypotheses regarding alcohol abuse, alcoholism, and associated RDS behaviors.

Continuous use of drug agents disrupts the circadian pattern of addiction behavior and alters the shift of addiction time. Experimentally, healthy individuals desired alcohol addiction in the early evening. However, individuals with alcohol use disorder (AUD) showed alcohol cravings during the early morning. This indicates the circadian dysfunction-mediated deregulation of addiction behavior.[120] Contrastingly, Webb et al reported that self-administration of drugs in animal experiments showed a preference for drug intake during the active phase of their daily activity (at night); however, drug tolerance altered the shift (daytime) of drug use.[121] Perreau-Lenz and Spanagel also reported that clock gene knock-out animals exhibited an altered rhythm of alcohol sensitivity.[122]

Previously, we proposed that darkness-induced alcohol consumption is associated with serotonin-melatonin pathway and dopaminergic regulation of the brain's mesolimbic pathways, which involves in alteration of neuronal expression in response to extended photoperiods that affect gene expression.[118] Starting from the late evening, serotonin can convert to melatonin, thereby reducing dopaminergic function and increased craving behavior.[123] It is commonly known that serotonin levels in the brain, particularly in the pineal gland, are the lowest during the dark phase. This is because, at night, the conversion of serotonin to melatonin, via adenylate cyclase-induced activation of N-Acetyltransferase. Pineal melatonin levels, in particular, are low during the daytime, surge five to tenfold at night, decline during a light pulse at night, and increase rapidly to night levels after the light–dark transition. It is important to note that melatonin also modulates the circadian rhythm of the endogenous opioid system (EOS). Moreover, melatonin was found to augment the EOS during the dark phase by raising the concentration of enkephalins in the hippocampus and hypothalamus of rat brains, while during periods of constant light, the absence of melatonin caused a decline in the tissue concentration of enkephalins. This may be important for comprehending the role of the inhibitory impact of enkephalins on GABA neurons, resulting in the altered release of dopamine during photoperiods, which may impact addiction behavior. Enkephalins mainly act through the mu and delta opioid receptors. Enkephalins modulate neurotransmission to regulate reward-related behaviour such as drug seeking. Alternatively, drug abuse also increases enkephalins in the reward pathway. Activation of opioid receptors (mu, delta and others) is responsible for drug-induced behaviour and reward-related activities.[124–126] In this case, this has important relevance to the finding of polymorphisms in genes that regulate mu-opioid receptors. SNP in mu opioid receptor gene OPRM1 (A118G) increase 3 fold binding affinity of endogenous opioids and also contributes to the susceptibility of opioid dependency.[127–129]

Treatment Strategies

The success rate of addiction treatment is not impressive. Dropout rates are high during treatment regimens, and there is a chance of relapse every time. The efficacy of the treatment depends on the activity of the circadian reward pathways. Blum et al developed a protocol "precision behavioral management" of SUD. They reported that replacement therapy reduces harm of opioid use. However, there is no sign of restoration of balance of neurotransmitters in the brain reward pathway. They suggested some approaches. Genetic assessment of polymorphic gene can give early predisposition to SUD. Study of RDS may be the essential tools in the treatment process. Application of dopaminergic agonist KB220 can maintain the gene expression in the brain reward pathway. Detection of mRNA expression of target polymorphic DNA

during treatment period exhibits effectiveness of the treatment. Comprehensive analysis of reported drugs (CARD) shows treatment conformity and avoidance record of illicit drugs.[130] Blum et al also proposed a unique therapeutic strategy for the treatment of RDS and SUD. A combination of enkephalinase inhibitor, enkephalin and dopamine secreting neuronutrients can maintain dopamine homeostasis and prevent RDS. This strategy can potentially resist the development of opioid use disorder.[131]

Pharmacological agents are used in the treatment purpose. High drinking in the dark (HDID) model is the most effective process for screening of new drug for therapeutic purposes. Application of acamprosate and baclofen ($GABA_B$ receptor agonist) in HDID mice decreased binge-like drinking.[132] Naltrexone (competitive antagonist of opioid receptors) decreased ethanol consumption in C57BL/6J mice during study through drinking in the dark (DID) model.[133] Gupta et al studied the effect of acamprosate and MPEP (metabotropic glutamate 5 receptor antagonist) on ethanol intake in C57BL/6J mice. MPEP reduced alcohol consumption more potentially than the effect of acamprosate.[134] Currently, FDA approved 3 drugs naltrexone, disulfiram, acamprosate for the treatment of drug addiction. The effectiveness of treatment is age-sensitive. Elderly adults show greater tolerability for naltrexone and disulfiram, but benzodiazepines have more efficacy.[135]

A clinical study was conducted on 22 participants where naltrexone was used for the treatment of SUDs (alcohol and opioid). Participants showed positive approaches about the treatment. However, some alternative experiences were also available in this study.[136] Exenatide was used in a randomized, double-blinded, placebo-controlled clinical trial on AUD participants. Exenatide is an incretin mimetic. It acts as a glucagon-like peptide-1 (GLP-1) receptor agonist. In this trial 2 mg exenatide was applied subcutaneously (once per week) on 127 AUD patients for 26 weeks. The result indicated that there was no significant reduction in heavy drinking days after exenatide treatment. However, exenatide prevented alcohol craving reactivity. Functional magnetic resonance imaging (fMRI) study showed that exenatide attenuated the function of the ventral striatum and septal area of the brain. These areas are responsible for drug reward and addiction.[137] A placebo controlled clinical trials (NCT03232112) was conducted on opioid dependent patients. 2 mg and 8 mg buprenorphine was given sublingually to 60 and 30 opioid dependent participants, respectively. Additionally, 60 volunteers were receiving placebo in this study. The result showed that there was an improvement in opioid use.[138] Another clinical trial (ANZCTR12618001759280) was done on opioid patients. This randomized clinical trial was conducted on 119 participants, suffering from opioid dependency. Buprenorphine was given monthly in 60 patients in subcutaneous depot, and another 59 patients received the same drug sublingually for 24 weeks. Better treatment satisfaction was observed in participants receiving subcutaneous depot of buprenorphine compared to patients receiving sublingually.[139]

A survey was conducted on non-commercial nighttime weekend drivers. This survey was mediated through AUD questionnaires on 1414 participants in USA. The results indicated that most of the drivers belonged to heavy drinkers without any clinical sign. Behavioral intervention could reduce the episodes of excessive consumption and also decreased the risk of crashes.[140] Alcohol withdrawal starts different complications, including circadian rhythm misalignment, endocrine dysfunction, and behavioral activities. Rosenwasser reported that alcohol withdrawal in human showed depressive behavior because alcoholic activity exerted anti-depressant effect. It was suggested that alcohol may alter the serotonergic activity in circadian pacemaker and impacts chronobiological effects. However, several chronobiological approaches are tried to treat SUD.[141]

Drug consumption affects circadian activity, sleep-wake cycle, and core clock gene expression. Regulation of circadian activity maintains sleep-wake cycle, metabolic activities, and morningness, which prevent addiction behavior. Application of light therapy, and melatonin prevent the risk of relapse.[37] Chronotherapy can be a treatment strategy to prevent drug addiction. Chronotherapy increases the success rate of the treatment of circadian dysfunction, sleep disorders, and psychiatric diseases. Chronotherapeutics target the molecular clock to improve circadian functions.[142] Agents of chronotherapy modulate behavioral activity and drug seeking. Application of benzodiazepine (BDZ) in the morning gives better results against alcohol withdrawal because the absorption rate is higher in the morning episode than in evening administration.[143] The expression of mixed-function oxidase, and serotonin transporters maintains a circadian rhythm and is implicated in the treatment of drug addiction and sleep disorders.[144] The expression of μ-opioid receptors, tyrosine hydroxylase, and the activity of dopaminergic signaling are under the control of the circadian system. Thus,

a chronotherapeutic approach against alcohol and drug abuse can increase the efficacy of the treatment. This approach may restrict drug seeking, drug intake, and drug craving. So, clinicians can follow two strategies for pharmacotherapies - a) use of therapeutics to decrease drug-seeking, and b) choice of administration time for maximum drug absorption and efficacy. Melatonin agonists and light therapy help in the normalization of circadian rhythms, which may be considered a therapeutic strategy. Administration of melatonin prevents morphine addiction, tolerance, and dependence in animals.[145] Vengeliene et al suggested that melatonin application at the end of the active cycle in rats decreased alcohol drinking and craving.[36] However, contradictory report is also available.[119] Melatonin acts on BDZ receptors and inhibits dopaminergic signaling of the reward pathway.[146] This effect may be associated with the GABAergic system of the melatonin pathway. Thus, melatonin is a drug choice for preventing drug seeking, dependence, and CRSDs. Naltrexone, an opioid antagonist restores circadian rhythmicity and can be used for therapeutic purposes. However, the timing of drug application is most important. Maximum expression of beta-endorphin (endogenous opioid) and the opioid receptors occur at night, and the taking of alcohol and drugs in the evening exerts reward effects. Thus, the use of naltrexone in the late evening exerts more effects on circadian rhythmicity and blocks the drug-associated reward effect, leading to greater efficacy of the treatment.[19] Sometimes treatment shows adverse effects. Buprenorphine and methadone affect the circadian and sleep cycle. Methadone exhibits phase-shifting and withdrawal effects.[19]

Inhibition of CK1ε/δ increases the persistency PER2 that restores circadian rhythmicity and blocks alcohol relapse and opioid craving.[60,147] Dopamine- and cAMP-regulated phosphoprotein, Mr 32 kD (DARPP32) regulates the dopaminergic and glutamatergic signaling. CK1ε/δ has effects on this phosphoprotein, and CK1ε/δ inhibitor exerts an indirect effect on this activity.[148] Acamprosate blocks hyperglutamatergic state and alcohol abuse.[59] Some drugs act on SCN to restore circadian rhythm. The application of methamphetamine restores circadian rhythmicity and is effective against drug addiction.[149] Another important enzyme is glycogen synthase kinase 3 beta (GSK3β), which phosphorylates various circadian proteins and shortens the circadian period.[150,151] Lithium, a potent inhibitor of GSK3β, increases the length of the circadian period but inhibits dopaminergic signaling that adversely increases alcohol consumption.[152] Moreover, exercise and bright light therapy restore circadian rhythm and decrease drug addiction.[153,154] Bright light improves the activity of the serotonergic system, which may be effective.[155] Weinstock et al proposed that exercise therapy could be adjunctive therapy against drug abuse.[156]

Pettorruso et al proposed a non-invasive process for the treatment of SUD without use of any chemical therapeutic agent. Repetitive transcranial magnetic stimulation (rTMS) repairs the dysfunction of specific reward system to prevent addiction behaviour. rTMS may protect hedonic pathway and decrease craving of addictive agents.[157] Currently, gene therapy and stem cell therapy are considered as the newer techniques for the therapeutic approaches of addiction disorders. Stem cell therapy can restrict alcohol addiction. Administration of human mesenchymal stem cells (hMSCs) into the lateral ventricle of the mouse brain restricts chronic alcohol consumption by up to 70% and also decreases the chance of relapse of alcohol consumption.[158]

Conclusion

In the present scenario, circadian rhythm dysfunction is a regular event in our modern society due to shift work, night work, exposure to bright light at night, internet and smartphone use, and jet lag. Circadian rhythm dysfunction has negative effects on human health, particularly neural activities, neuroendocrine functions, and metabolic activities. Drugs can resynchronize circadian rhythms and improve addiction behavior. Some researchers claim that the application of melatonin and melatonin-receptor agonists is considered to be better against drug abuse; however, significant contradictions are also available and suggest the negative impact of melatonin against alcohol addiction. Bright light therapy may also restore circadian rhythm and be effective on the reward system. Thus, a non-pharmaceutical treatment regimen can improve drug addiction behavior. Extensive research on neuroscience, chronobiology, genetics, and socio-behavioral studies will explore the physiological basis of addiction behavior and also open new window for the development of effective treatment against SUD. RDS is a crucial factor in SUD. Expression of opioid receptors, endogenous enkephalin levels and dopamine homeostasis are associated with RDS. Strategy on RDS-dependent treatment has strong basis for reducing the burden of addiction behavior, which can be beneficial for individuals, their families, and society. Chronotherapy like light therapy, dark therapy, wake therapy are effective against psychiatric disorders. These treatment

strategies can bring new hope to counteract SUD also. There are several strategies in the treatment purpose, but clinical research and trials are still behind. Sufficient clinical trials are must be needed to establish the effectiveness of treatment procedure. Finally, it can be said that public awareness about circadian dysfunction and drug addiction can give fruitful results in preventing drug seeking and drug abuse in the near future.

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This review article is prepared on the basis of literature survey. So, no new data has been generated.

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