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Circadian Rhythms and Addiction: Mechanistic Insights and Future Directions

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Circadian rhythms are prominent in many physiological and behavioral functions. Circadian disruptions either by environmental or molecular perturbation can have profound health consequences, including the development and progression of addiction. Both animal and humans studies indicate extensive bidirectional relationships between the circadian system and drugs of abuse. Addicted individuals display disrupted rhythms, and chronic disruption or particular chronotypes may increase the risk for substance abuse and relapse. Moreover, polymorphisms in circadian genes and an evening chronotype have been linked to mood and addiction disorders, and recent efforts suggest an association with the function of reward neurocircuitry. Animal studies are beginning to determine how altered circadian gene function results in drug-induced neuroplasticity and behaviors. Many studies suggest a critical role for circadian rhythms in reward-related pathways in the brain and indicate that drugs of abuse directly affect the central circadian pacemaker. In this review, we highlight key findings demonstrating the importance of circadian rhythms in addiction and how future studies will reveal important mechanistic insights into the involvement of circadian rhythms in drug addiction.

Keywords: circadian rhythms, addiction, reward, dopamine, alcohol

A growing body of literature connects perturbations in circadian rhythms and the genes that control the molecular clock to the development and progression of addictive disorders. Clinical studies have found that individuals with addictive disorders have highly disrupted rhythms, and it is likely that genetic and/or environmental disruptions to the normal sleep/wake cycle increase the vulnerability for addiction (Bolelli et al., 1979; Conroy et al., 2012; Fakier & Wild, 2011; Kovanen et al., 2010; Sjöholm et al., 2010; Vescovi, Coiro, Volpi, & Passeri, 1992). Conversely, self-medication through drug or alcohol abuse is considered to be an attempt to ameliorate sleep- and mood-related problems found with general circadian rhythm disruption (Staddon, 2013). Several studies have also found that an evening chronotype (i.e., "night owls") is associated with higher rates of depression, sleep problems, and substance abuse (Adan, 1994; Broms et al., 2011; Fisk & Montgomery, 2009; Levandovski et al., 2011). During adolescence, there is a natural shift toward an evening preference, which coincides with the developmental window in which individuals are most vulnerable to mood and addiction disorders (Hasler & Clark, 2013). One concept put forth to help understand these phenotypes is the "social jet lag hypothesis." Social jet lag occurs when an individual is up early for work or school during the week and then sleeps late on the weekends, creating a situation that is similar to flying overseas and back each week (Hasler & Clark, 2013; Touitou, 2013; Wittmann, Dinich, Merrow, & Roenneberg, 2006). Studies generally find correlations between the degree of social jet lag, depression, and drug and alcohol use (Foster et al., 2013; Hasler & Clark, 2013; Wittmann et al., 2006). More work is necessary to determine the importance of circadian misalignment to the vulnerability for addiction. The increased impulsivity of night owls and adolescents also often puts them into situations in which drug and alcohol use is prevalent and may predispose them to substance abuse (Selvi et al., 2011; Stautz & Cooper, 2013). Additionally, although environmentally derived circadian disturbances (i.e., shift work) have been associated with heightened risk for substance abuse (Bildt & Michelsen, 2002), it is difficult to determine if these effects can be attributed to circadian misalignment per se or the effects of stress or other predisposing factors. Furthermore, we now know that circadian genes are directly involved in the regulation of dopaminergic reward circuitry (Akhisaroglu, Kurtuncu, Manev, & Uz, 2005; Schade et al., 1995; Shieh, Chu, & Pan, 1997; Sleipness, Sorg, & Jansen, 2007b; Weber, Lauterburg, Tobler, & Burgunder, 2004); thus, disruptions to the circadian system change the reward value and motivation for addictive substances through direct effects on reward circuits (Abarca, Albrecht, & Spanagel, 2002; Andretic, Chaney, & Hirsh, 1999; Liu et al., 2005; McClung et al., 2005; Roybal et al., 2007; Spanagel, Pendyala, et al., 2005; Zghoul et al., 2007). This regulation by the circadian system is through both indirect projections

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from the master pacemaker of the suprachiasmatic nucleus (SCN) to the ventral tegmental area (VTA), and through local circadian gene expression within dopaminergic neurons (Luo & Aston-Jones, 2009; McClung, 2007a; Sleipness et al., 2007b). Thus it appears that vulnerability to addiction is dependent on the circadian system in multiple ways.

Once an individual starts abusing drugs or alcohol, this exposure produces both acute and lasting changes to circadian rhythms and sleep, creating a vicious cycle for someone who already started with a circadian rhythm abnormality (Irwin, Valladares, Motivala, Thayer, & Ehlers, 2006; Jones, Knutson, & Haines, 2003; Morgan et al., 2006; Shibley, Malcolm, & Veatch, 2008; Wasielewski & Holloway, 2001). These changes to rhythms and sleep persist even after administration of the abused substance has stopped, and this very often contributes to relapse. Indeed, insomnia is the most common complaint from alcoholics after they stop drinking (Spanagel, Rosenwasser, Schumann, & Sarkar, 2005; Zhabenko, Wojnar, & Brower, 2012). It is possible that circadian rhythm and sleep stabilization would help decrease addiction vulnerability and/or reduce the risk for relapse in those with addictive disorders (Arnedt, Conroy, & Brower, 2007; Brower et al., 2011). Thus, it is important to understand how circadian rhythm disruptions lead to increased vulnerability for addiction, and what changes occur to the molecular clock following chronic drug use. This review will focus on studies aimed at understanding the influence of specific circadian genes, as well as rhythm disruptions as a whole, on addiction-related behavior. We will also discuss some of the mechanisms by which circadian genes regulate reward-related pathways in the brain, altering the response to drugs and alcohol. Finally, we will highlight some of the changes that occur in circadian gene expression in response to drugs and alcohol and what studies are needed moving forward to advance our understanding of the connection between the circadian system and reward.

The Molecular Clock

At the cellular level, circadian rhythms are generated by 24-hr autoregulatory transcriptional/translational feedback loops consisting of "circadian" genes and their protein products (Bae et al., 2001; Jin et al., 1999; Shearman, Zylka, Reppert, & Weaver, 1999). In mammals, the feedback loop begins in the cell nucleus where Circadian Locomotor Output Cycles Kaput (CLOCK), or Neuronal PAS Domain Protein 2 (NPAS2), and Brain and Muscle ARNT like Protein 1 (BMAL1) proteins heterodimerize and drive the transcription of the *Period* (*Per1*, *Per2*, and *Per3*) and *Cryptochrome* (*Cry1* and *Cry2*) genes by binding to the E-box (CACGTG) domain on their gene promoters. When CLOCK expression is low in the SCN, NPAS2 compensates to regulate normal circadian transcription (DeBruyne et al., 2006). Under normal conditions, NPAS2 is largely expressed in the forebrain and liver, with very little expression in the SCN (Bertolucci et al., 2008; DeBruyne, Weaver, & Reppert, 2007; O'Neil et al., 2013; Reick, Garcia, Dudley, & McKnight, 2001). Once translated, PER and CRY proteins build in the cytoplasm of the cell over the course of the day and eventually form hetero- and homodimers that feed back to the cell nucleus to inhibit CLOCK(NPAS2):BMAL1-mediated transcription. The timing of nuclear entry is balanced by regulatory kinases that phosphorylate the PER and CRY proteins, leading to their degradation (Lowrey & Takahashi, 2000; Mohawk & Takahashi, 2011; Wang, Ko, Koletar, Ralph, & Yeomans, 2007). CRY1 and CRY2 degradation is also regulated by FBXL3, which regulates the period and robustness of the clock (Busino et al., 2007; Godinho et al., 2007; Shi et al., 2013). The molecular clock regulates two other promoter elements, DBP/E4BP4 binding elements (D boxes) and REV-ERBα/ROR binding elements (RREs; Ueda et al., 2005). REV-ERBα, an orphan nuclear receptor, negatively regulates the activity of the CLOCK:BMAL1. The same mechanism controlling *Per* and *Cry* gene transcription also controls transcription of REV-ERBα. Similarly, the transcription factor DPB is positively regulated by the CLOCK:BMAL1 complex (Ripperger & Schibler, 2006) and acts as an important output mechanism, driving rhythmic transcription of other output genes via a PAR basic leucine zipper (PAR bZIP) (Lavery et al., 1999). In addition to these cyclical feedback loops, clock-controlled genes (CCGs) present in the CNS and periphery are regulated in a similar fashion, via E-Box-mediated transcription. In this manner, the clock gene machinery regulates the rhythmic control of countless genes in the brain and periphery. Indeed, between 10% and 15% of all transcripts in various tissues exhibit circadian rhythms and are believed to be directly controlled by the molecular clock (Duffield et al., 2002; Panda, Hogenesch, & Kay, 2002; Storch et al., 2002).

Circadian Gene Mutations, Cocaine Seeking, and Reward

In clinical studies, patients with substance abuse disorders exhibit disturbances in sleep patterns and circadian rhythms, indicating that drug use may perturb the circadian system and/or disturbances in the circadian system may contribute to the development of drug dependence. Association studies in clinical populations between clock gene polymorphisms and substance abuse disorders have been useful in determining if circadian disruptions are risk factors for addiction susceptibility. Malison and colleagues initially determined that there was no association between CLOCK, PER1, or PER2 single-nucleotide polymorphisms (SNPs) and susceptibility to cocaine addiction (Malison, Kranzler, Yang, & Gelernter, 2006). A caveat of this study, however, is that all patients comorbid for other psychiatric diseases, including bipolar disorder and depression, were excluded from the addiction cohort. The extensive associations between clock gene polymorphisms and mood disorders likely excluded many patients that would yield significant differences in clock gene SNPs compared with healthy controls. A subsequent study of polymorphic repeat variation of the *Per2* gene using variable number tandem repeat (VNTR) analysis determined that variation in repeat allele frequencies in intron 3 of the *Per2* gene was significantly associated with vulnerability to cocaine addiction (Shumay, Fowler, et al., 2012). Interestingly, the shorter allele, which was characteristic of the cocaine abusers, was also associated with lower D2R availability (Shumay, Fowler, et al., 2012), which is consistently associated with an increased risk for drug addiction (Volkow, Wang, Fowler, Tomasi, & Telang, 2011). This raises the intriguing possibility that a *Per2* mutation may in turn lead to the disruption of D2R, although such associative studies are limited in interpreting the directionality of these effects. Preclinical studies that can utilize molecular techniques to systematically disrupt clock gene function have provided insight into the potential causal connection between circadian disturbances and limbic function.

The molecular components of the circadian clock described above are widely expressed throughout the brain, including the mesocorticolimbic system central to reward processing and susceptibility to drugs of abuse (Reppert & Weaver, 2002; Rosenwasser, 2010). Consequently, these nuclei exhibit circadian patterns of activity in neuronal firing and neurochemical transcription and release in mice and rats (McClung, 2007b), suggesting functional regulation of the circadian system over these processes. Additionally, many behaviors associated with the limbic system, including drug-seeking behavior and locomotor sensitization, exhibit rhythmic patterns despite no change in the metabolic rates of the drugs themselves (Akhisaroglu et al., 2005; Baird & Gauvin, 2000). Collectively, these phenomena point to a direct connection between circadian gene expression and reward, leading to the possibility that disruptions in the circadian system may directly affect risk for drug dependence and addiction.

Clock

The circadian gene, *Clock*, is expressed in the VTA and nucleus accumbens (NAc) (McClung et al., 2005; Uz, Akhisaroglu, Ahmed, & Manev, 2003) and has been implicated in modulating reward processing, providing a candidate target for ameliorating critical risk factors in models of addiction and bipolar disorder. Polymorphisms in the *Clock* gene are associated with aberrant behavioral outcomes in mice and humans, including manic phenotypes and profound increases in drug-seeking behavior (Benedetti et al., 2003; Roybal et al., 2007; Table 1). Specifically, mice harboring a mutation in the *Clock* gene that results in a 51-amino acid deletion of exon 19 (*Clock*Δ19), eliminating the transactivational domain sequence (King et al., 1997), exhibit a number of behavioral responses to cocaine that are associated with a hyperhedonic phenotype. The characterization of mesolimbic alterations associated with this mutation lends insight into the mechanisms by which the *Clock* gene normally regulates reward circuitry and can uncover candidate targets connecting mutations in circadian genes to aberrant reward processing. *Clock*Δ19 mice exhibit a conditioned place preference for cocaine (CPP) at a dose that is lower than that which is sufficient to generate a CPP response in wild-type (WT) littermates (McClung et al., 2005). Additionally, *Clock*Δ19 mice exhibit decreased acquisition latency and increased intake of cocaine under an FR1 self-administration paradigm compared with WT mice (Ozburn, Larson, Self, & McClung, 2012). *Clock*Δ19 mice also exhibit significantly higher cocaine breakpoints under a progressive ratio schedule, collectively indi-

Table 1
Phenotypes of Circadian Gene Mutant Mice

Genotype	Background	Circadian phenotype (DD)	Drug behaviors	References
*Clock*Δ19	BALB/c	Longer period; arrhythmic	Cocaine: hypersensitization, increased CPP, reduced latency to acquire self-administration, and increased seeking and motivation Alcohol: elevated two-bottle choice drinking and preference, hypersensitive to sedative effects (LORR)	McClung et al., 2005; Ozburn et al., 2012; Vitaterna et al., 1994;
$Per1^{Brdm1}$	$129SvEv^{Brd}$/C57BL/6-$Tyr^{c\text{-}Brd}$	Shorter period; rhythmic	Cocaine: normal sensitization and self-administration and reinstatement, abolished CPP Alcohol: normal sensitivity to sedative effects (LORR), normal seeking, reinstatement, and alcohol deprivation effect, elevated two-bottle choice drinking following social defeat stress	Abarca et al., 2002; Dong et al., 2011; Halbout et al., 2011; Zghoul et al., 2007
$Per2^{Brdm1}$	$129SvEv^{Brd}$/C57BL/6-$Tyr^{c\text{-}Brd}$	Shorter period; becomes arrhythmic	Cocaine: hypersensitization, normal CPP Alcohol: elevated two-bottle choice drinking and preference, increased seeking and motivation, hypersensitive to sedative effects (LORR) Morphine: reduced tolerance and withdrawal	Perreau-Lenz et al., 2009, 2010; Spanagel, Rosenwasser, et al., 2005
$Per1^{Brdm1}$	C57BL/6J	Shorter period; rhythmic	Alcohol: elevated two-bottle choice drinking and preference, increased CPP	Gamsby et al., 2013
$Per2^{Brdm1}$	C57BL/6J or C57BL/6-$Tyr^{c\text{-}Brd}$	Shorter period; becomes arrhythmic	Alcohol: elevated two-bottle choice drinking and preference that is not increased by chronic restraint stress, increased CPP	Brager et al., 2011; Gamsby et al., 2013; Logan et al., 2012

Note. CPP = conditioned place preference for cocaine; DD = constant darkness; LORR = loss of righting reflex.

cating that this mutation increases the motivational and reinforcing properties of cocaine (Ozburn et al., 2012). These results are striking given the typically low drug self-administration behavior in BALB/c mice, the background on which these mice are bred. The consistent behavioral profile in *Clock* mutant mice across paradigms in the context underscores the critical role of the *Clock* gene in modulating cocaine reward in WT animals.

Period Genes

Disruptions in the *Period* (*Per*) genes yield different behavioral outcomes in measures of cocaine reward and sensitization. Although the psychomotor responses to acute cocaine injections in *Per1* or *Per2* mutant mice do not differ from WT littermates, chronic cocaine administration results in different levels of behavioral sensitization (Abarca et al., 2002). *Per1* mutant mice do not show locomotor sensitization to repeated cocaine injections compared with WT controls, which is comparable to the response of *Drosophila* with a mutation in the *Period* genes (Andretic et al., 1999), suggesting a conserved influence of *Per1* on behavioral sensitization. Conversely, *Per2* mutant mice exhibit enhanced locomotor sensitization to cocaine compared with WT and *Per1* mice (Abarca et al., 2002). In WT mice, striatal PER1 rhythms are associated with changes in cocaine sensitization, where high *Per1* expression is associated with high cocaine sensitization (Uz et al., 2003). Moreover, cocaine sensitization diminishes during the night when striatal *Per1* expression is at its nadir (Uz et al., 2003). If *Per1* rhythms in melatonin-proficient mice are abolished through pinealectomy, this results in a loss of diurnal rhythms in sensitization. These results, along with the presence of melatonin receptors in the striatum, indicate that pineal hormones directly influence striatal *Per1* rhythms and cocaine sensitization and that the rhythm in *Per1* expression is critical for diurnal differences in behavioral sensitization (Uz et al., 2003). Given that behavioral sensitization is thought to be a critical component of drug craving that leads to dependence (Robinson & Berridge, 1993), understanding the precise connection between the circadian system and drug sensitization will lend insight into the influence of circadian disturbances as a risk factor for drug taking and addiction.

In addition to the differential effects of *Per1* and *Per2* on cocaine sensitization, *Per1* and *Per2* mutant mice exhibit opposing CPP responses to cocaine, whereas *Per1* mice do not show cocaine CPP compared with WT or *Per2* mice (Abarca et al., 2002). In contrast, *Per2* mice exhibit a significant place preference to cocaine, although this does not differ from WT mice, suggesting the role of *Per2* in regulating locomotor responses to cocaine may differ from its role in processing its hedonic value (Abarca et al., 2002). Interestingly, further examination of drug-seeking behavior in *Per1* mutant mice found that this mutation does not abolish motivation for cocaine self-administration or cocaine reinstatement following extinction (Halbout, Perreau-Lenz, Dixon, Stephens, & Spanagel, 2011). These differences suggest that each circadian gene mutation may differentially modulate cocaine reward depending on the paradigm used. This discrepancy adds to the voluminous body of literature indicating distinct neural substrates may underlie various components of drug reward. Unlike *Clock*Δ19 mice, which exhibit alterations in both cocaine CPP and self-administration (McClung et al., 2005; Ozburn et al., 2012), the role of *Per1* in regulating cocaine reward clearly depends on the particular behavioral paradigm measured, for example, whether the drug administration is passive or active. This also suggests that *Per1* may regulate subcomponents of the neurobiological underpinnings of reward. Indeed, the potential mechanisms by which circadian genes regulate mesolimbic circuitry are numerous, and therefore, global circadian gene mutations likely involve pleiotropic effects on reward-related processing.

Circadian Gene Mutations and Alcohol Seeking and Reward

Human clinical studies suggest bidirectional relationships between alcoholism and circadian rhythms. Excessive alcohol drinking may disrupt circadian rhythms, while circadian disruption or desynchrony may promote and maintain excessive alcohol drinking (Spanagel, Rosenwasser, et al., 2005). In chronic alcoholics, circadian disruption is known to persist during extended periods of abstinence (Drummond, Gillin, Smith, & DeModena, 1998; Landolt & Gillin, 2001), which may precipitate relapse to drinking (Brower, 2003; Brower, Aldrich, Robinson, Zucker, & Greden, 2001). On the other hand, alterations to sleep–wake cycles, among other rhythms, may predict initial susceptibility to alcohol abuse and alcoholism (Crum, Ford, Storr, & Chan, 2004; Crum, Storr, Chan, & Ford, 2004) Circadian desynchrony itself may be a risk factor for alcoholism (Härmä, Tenkanen, Sjoblom, Alikoski, & Heinsalmi, 1998; Trinkoff & Storr, 1998). Human genetic studies have found mutations in a few of the circadian genes that are associated with alcohol addiction (Comasco et al., 2010; Dong et al., 2011; Spanagel, Pendyala, et al., 2005). Evidence from circadian mutant mice have begun to uncover the role of these genes in alcohol-related behaviors.

Period Genes

Several studies have suggested the role of *Per2* in alcohol-drinking behavior in humans and animal models (Table 1). Schumann and colleagues were the first to demonstrate that an SNP in *Per2* (rs56013859) was associated with high levels of alcohol drinking in alcohol-dependent patients (Spanagel, Pendyala, et al., 2005). Interestingly, this SNP is not associated with the amount of alcohol consumed, or measures of alcohol misuse, among social drinkers (Kovanen et al., 2010), suggesting *Per2* has a specific role in alcohol dependence. Although direct biological significance of this SNP is unknown, it is hypothesized to reduce *Per2* gene expression by impairing transcription factor binding (Partonen et al., 2007; Spanagel, Pendyala, et al., 2005). Evidence from *Per2* mutant mice ($Per2^{-/-}$) further supports *Per2* as a candidate gene for elevated alcohol intake. $Per2^{-/-}$ mice consume high levels of alcohol and display increased preference for alcohol at higher concentrations and alcohol-seeking behaviors and elevated behavioral sensitivity to acute alcohol administration (Brager, Prosser, & Glass, 2011a; Perreau-Lenz, Zghoul, de Fonseca, Spanagel, & Bilbao, 2009; Spanagel, Pendyala, et al., 2005). These behavioral phenotypes seem to persist regardless of genetic background, indicating that the *Per2* mutation has high penetrance (Gamsby et al., 2013).

$Per2^{-/-}$ mice also show brain hyperexcitability caused by decreased efficiency to clear synaptic glutamate and elevated dopamine (DA) levels in the striatum (Hampp et al., 2008), which may

contribute to their elevated alcohol intake (Spanagel, Pendyala, et al., 2005). Acamprosate (Campral), a pharmacological treatment for relapse in recovering alcoholics, is thought to exert its therapeutic effects by attenuating hyperglutamatergic signaling induced by repeated binge and withdrawal episodes (Spanagel & Kiefer, 2008; Spanagel, Rosenwasser, et al., 2005). Acamprosate reduces extracellular glutamate levels in the brain and reduces alcohol drinking during free-choice (Brager, Prosser, & Glass, 2011b; Spanagel, Rosenwasser, et al.,2005) and relapse paradigms in *Per2*$^{-/-}$ mice (Brager et al., 2011a). These effects appear to be independent of alterations to locomotor and drinking rhythms (Brager et al., 2011a; Gamsby et al., 2013), suggesting acamprosate's ability to reduce alcohol drinking may not involve direct modulation of the circadian pacemaker. However, infusion of acamprosate directly into the SCN in *Per2*$^{-/-}$ mice reduced alcohol intake during a relapse paradigm that was similar to the reductions observed after infusion into the VTA, NAc, or peduculopontine tegmentum (PPT; Brager et al., 2011b). It will be important to determine whether acamprosate reduces alcohol drinking by altering or modulating synaptic communication between circadian and reward-related neurocircuitry.

The majority of human studies reporting associations between circadian gene polymorphisms and alcohol drinking have revealed novel interactions between genes and environment or other psychiatric disorders. Several recent genetic studies from the Mannheim Study of Children at Risk, a large ongoing epidemiological cohort study of the outcome of early risk factors from infancy to adulthood (Dong et al., 2011), link polymorphisms in circadian genes with alcohol use and stress. The roles of *Per1* and *Per2* in stress-related alcohol drinking may involve both the development of compulsive alcohol drinking in adolescents and the maintenance of heavy alcohol drinking in adults. An SNP in the *Per1* promoter (rs3027172) is associated with heavy drinking among adolescents and alcohol-dependent adults (Dong et al., 2011). Among heavy drinking adolescents exposed to high psychosocial stress, the rs2037172 genotype (minor C allele), was significantly associated with both frequency of drinking and the amount of alcohol consumed (Dong et al., 2011). Similarly, adolescents homozygous for the major A allele of the *Per2* rs56013859 genotype were more likely to report harmful and risky alcohol-drinking patterns if they were exposed to high stress in both "experienced" and "inexperienced" alcohol users (Blomeyer et al., 2013) and were more likely to report disrupted sleep (Comasco et al., 2010). Stress-related psychiatric disorders are also quite high among alcoholics, and comorbid anxiety and depression disorders often lead to relapse drinking (De Witte, Pinto, Ansseau, & Verbanck, 2003; Driessen et al., 2001). As circadian gene mutations are also associated with mood disorders (Kennaway, 2010), these could be an underlying contributor to heightened stress response, alcohol drinking, and anxiety and depression.

Animal studies suggest that lowered *Per* gene function is associated with elevated alcohol drinking, increased anxiety-like behaviors, and altered stress response. However, the effect of either the *Per1* or *Per2* mutation on alcohol and anxiety-like behaviors requires more systematic study because the penetrance of the mutation seems to depend on genetic background of the mouse. When the *Per1* mutation is backcrossed to a high alcohol-preferring C57BL/6J background, these mice display elevated levels of alcohol intake and reward similar to the *Per2* mutation on either a mixed (129SvEv × C57BL/6) or pure (C57BL/6) background (Gamsby et al., 2013). In contrast, the *Per1* mutation on a mixed background fail to display increased alcohol drinking or lever pressing, elevated drinking following deprivation, or enhanced sensitivity to alcohol (Perreau-Lenz et al., 2009; Zghoul et al., 2007). However, *Per1*$^{-/-}$ mice on a mixed background consume more alcohol than WT animals following social defeat stress (Dong et al., 2011). Preliminary data suggests *Per2*$^{-/-}$ mice do not show an increase in alcohol drinking following repeated restraint stress (Sarkar, 2012). Additive effects of *Per1* and *Per2* knockdown on anxiety-like behaviors have been observed (Spencer et al., 2013), but not on alcohol drinking or reward (Gamsby et al., 2013), although genetic background may contribute to these discrepancies.

Systematic characterization of the *Per* mutant mice across multiple behavioral domains in combination with targeted brain region gene knockdown and overexpression approaches are necessary to better understand the role of *Per* genes in alcohol, anxiety, and depression phenotypes. There is very little known regarding the molecular mechanisms in the brain affected by changes in *Per* expression that give rise to changes in behavior. *Per* genes seem to be protective against elevated alcohol drinking under baseline and stress conditions. Glucocorticoid release following stress directly regulates the transcription of *Per1* and *Per2* by transcription factor binding to glucocorticoid receptor response elements and other binding motifs (Cheon, Park, Cho, & Kim, 2013; Pezük, Mohawk, Wang, & Menaker, 2012; Reddy, Gertz, Crawford, Garabedian, & Myers, 2012). The CC genotype identified in high-drinking, chronically stressed adolescents significantly reduces glucocorticoid induced transcriptional activation of *Per1* in human B-lymphoblastoid cells (Dong et al., 2011). Impaired *Per* gene upregulation in response to stress may affect downstream mechanisms that alter neuronal function and responses contributing to elevated alcohol drinking and dependence (Agapito, Mian, Boyadjieva, & Sarkar, 2010; Dong et al., 2011; Sarkar, 2012).

Clock

The *Clock* gene has also been identified as a potential candidate for alcohol addiction and comorbid disorders. Several polymorphisms in *Clock* are linked to alcohol dependence and depression, among other psychiatric disorders. However, studies have failed to find associations between any *Clock* polymorphism and alcohol dependence independent of other psychiatric disorders (Kovanen et al., 2010; Sjöholm et al., 2010). A haplotype formed by *Clock* SNPs rs3805151, rs2412648, rs2412464, and rs11240 was associated with an increased risk for comorbid depression and alcohol use disorders (Sjöholm et al., 2010). Among the SNPs within the haplotype, the most suggestive of the polymorphisms is rs11240, which is in linkage disequilibrium with rs1801260, a well-studied *Clock* SNP (3111T/C). The C allele is associated with bipolar disorder, schizophrenia, sleep disorders, evening chronotypes, and obesity (Barclay et al., 2011; Benedetti et al., 2007, 2003; McCarthy, Nievergelt, Kelsoe, & Welsh, 2012; Soria et al., 2010; Tsuchimine, Yasui-Furukori, Kaneda, & Kaneko, 2013; Zhang et al., 2011). This polymorphism is located within the 3′ untranslated region of the *Clock* gene, where it is likely to affect RNA stability or protein translation.

As mentioned previously, the *Clock*Δ19 mutant mice have an increase in dopaminergic activity in the VTA and exhibit increased cocaine preference, reward, and seeking behaviors (Coque et al., 2011; Ozburn et al., 2012; Roybal et al., 2007). They also exhibit reduced anxiety- and depression-like behavior, hyperhedonia, hyperactivity, circadian rhythm disruptions, and decreased sleep, which is similar to a "manic-like" behavioral state (Arey & McClung, 2012; Roybal et al., 2007). Indeed, substance use disorders, including alcohol, are often comorbid with bipolar disorder (Fossey et al., 2006; Regier et al., 1990). Many of the anxiety- and depression-like behaviors are rescued by restoring CLOCK expression specifically in the VTA or can be recapitulated by reducing CLOCK expression in the VTA (Mukherjee et al., 2010; Roybal et al., 2007). Recently, we demonstrated that *Clock* is also important for modulating alcohol intake and preference (Ozburn et al., 2013). *Clock*Δ19 mutant mice consume more alcohol and prefer alcohol at higher concentrations during two-bottle, free choice conditions than their WT littermates. Similar to other behaviors, *Clock* knockdown in the VTA of WT mice recapitulates the alcohol-preferring phenotype of *Clock*Δ19 mutant mice. *Clock*Δ19 mutant mice are also hypersensitive to the sedative effects of alcohol as well as ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist, but not pentobarbital, during both inactive and active phases (Ozburn et al., 2013). Unlike *Per2*$^{-/-}$ mice, acamprosate fails to reduce alcohol intake and preference in *Clock*Δ19 mutant mice (Ozburn et al., 2013; Spanagel, Pendyala, et al., 2005). Thus, glutamatergic transmission is involved in the sedative and hypnotic effects of alcohol, whereas altered dopaminergic transmission likely contributes to the elevated alcohol drinking in *Clock*Δ19 mice (McClung, 2007b; Ozburn et al., 2012; Spencer et al., 2012). A hyperdopaminergic state may also underlie the mood- and reward-related behaviors in these mice (Russo & Nestler, 2013).

Other Circadian Genes

Other circadian genes are implicated in human alcohol abuse and alcoholism and comorbid disorders. For example, SNPs in *Per3* are associated with sleep disruption, bipolar disorder, novelty seeking, and alcohol behaviors (Archer et al., 2003; Artioli et al., 2007; Benedetti et al., 2008; Kripke, Nievergelt, Joo, Shekhtman, & Kelsoe, 2009; Viola et al., 2007; Wang et al., 2012). Using BXD recombinant inbred mouse strains, a *cis*-acting expression quantitative trait locus (QTL) was mapped to *Per3* that is linked to stress, anxiety, and alcohol traits (Wang et al., 2012). *Per3* may have tissue-specific function in circadian rhythmicity (Pendergast, Niswender, & Yamazaki, 2012). In the mouse hippocampus, *Per3* regulates multiple downstream genes associated with circadian rhythms, stress response, synaptic functions, and alcoholism (Wang et al., 2012). Notably, one of those genes, calpastatin (*Cast*), was identified as a susceptibility gene for human alcohol dependence (Treutlein et al., 2009). A study from a population-based sample of controls and individuals with alcohol use disorder analyzing multiple SNPs failed to identify any significant associations between circadian genes and alcohol dependence (Kovanen et al., 2010). However, an SNP in *Arntl2* (*Bmal2*, rs4964057) was nominally associated with alcohol abuse, and *Arntl* (*Bmal1*, rs6486120) was nominally associated with alcohol abuse among social drinkers (Kovanen et al., 2010). Both *Bmal1* and *Bmal2* are involved in normal circadian rhythms (Shi et al., 2010). Polymorphisms in *Bmal1* have also been associated with bipolar and depressive disorders (Mansour et al., 2006; Utge et al., 2010); however, there have been few studies that have examined the role of *Bmal1* in drug-seeking behavior. Both in peripheral blood and mononuclear cells collected from alcohol-dependent and socially drinking individuals, *Bmal1* expression was significantly reduced (Ando et al., 2010; Huang et al., 2010). In chronically drinking animals, *Per* expression rhythms are altered in the hypothalamus (Chen, Kuhn, Advis, & Sarkar, 2004), but the effects of alcohol on *Bmal1* or *Bmal2* expression in mood- and reward-related brain regions are unknown. Disrupted or reduced expression of *Bmal1* or *Bmal2* could alter the transcriptional mechanisms driven by CLOCK and BMAL complexes that affect alcohol-drinking or withdrawal behaviors. Alcohol-related phenotypes have not been explored in BMAL1-deficient mice.

Both casein-kinase 1 epsilon and delta (CK1ε and CK1δ, respectively) are additional circadian genes tied to alcoholism and alcohol relapse (Al-Housseini et al., 2008; Perreau-Lenz et al., 2012). We will refer to both isoforms as CK1ε/δ because most studies do not distinguish between the two. Both isoforms belong to the superfamily of serine/threonine-specific kinases that play a major role in regulating and sustaining the pace of the molecular clock by phosphorylating circadian proteins, BMAL1, CRY, PER1, and PER2 (Eide, Kang, Crapo, Gallego, & Virshup, 2005; Meng et al., 2008). PER2 is rhythmically destabilized by CK1ε/δ phosphorylation (Eide et al., 2005; Etchegaray et al., 2009; Meng et al., 2008), and pharmacological inhibition of CK1ε/δ induces phase delays of circadian locomotor activity, enhances PER2 protein levels, and inhibits nuclear translocation of PER3 (Badura et al., 2007; Sprouse et al., 2010). CK1ε/δ inhibition also inhibits PER3 nuclear translocation (Sprouse et al., 2010). CK1ε/δ is associated with behavioral responses to other drugs of abuse (Bryant et al., 2009, 2012). In chronic alcoholics, CK1ε/δ protein levels are moderately elevated in the superior frontal cortex (Al-Housseini et al., 2008).

Pharmacological inhibition of CK1ε/δ in rats undergoing a relapse-like alcohol-drinking paradigm, during which chronic alcohol drinking is interrupted with repeated deprivation phases (Vengeliene, Bachteler, Danysz, & Spanagel, 2005), prevented the alcohol deprivation effect at higher doses with some nonspecific effects on water and saccharin consumption (Perreau-Lenz et al., 2012). CK1ε/δ inhibition attenuated the elevated alcohol intake during the day that is often observed during the reintroduction of alcohol following a period of deprivation and induced an almost 12-h phase shift in locomotor activity (Perreau-Lenz et al., 2012). CK1ε/δ inhibition also normalizes anxiety-like behaviors and has partial effects on depression-like behaviors, but not hyperactivity, in *Clock*Δ19 mutant mice (Arey & McClung, 2012). Future studies will determine if changes or stabilization of circadian rhythms are necessary for the therapeutic effects of CK1ε/δ inhibition on mood- and alcohol-related behaviors in *Clock*Δ19 mutant mice. More studies are needed to systematically probe alcohol-related phenotypes in mice with mutations in circadian genes.

Circadian Gene Mutations and Other Drugs of Abuse

Besides cocaine and alcohol, there are few studies specifically testing the role of circadian genes in the behavioral responses to

other types of drugs. Opiate-dependent patients often report sleep–wake disturbances (Oyefeso, Sedgwick, & Ghodse, 1997), and morphine withdrawal in rodents disrupts circadian behavioral rhythms (Caillé, Espejo, Koob, & Stinus, 2002; Stinus, Robert, Karasinski, & Limoge, 1998). Chronic opiate withdrawal enhances *Per2* gene and protein expression in the limbic forebrain and frontal cortex (Ammon, Mayer, Riechert, Tischmeyer, & Hollt, 2003; Ammon-Treiber & Hollt, 2005; Hood, Cassidy, Mathewson, Stewart, & Amir, 2011). $Per2^{Brdm1}$ mutant and WT mice responded similarly to acute morphine, but the mutant mice exhibited reduced tolerance to the analgesic and withdrawal effects (Perreau-Lenz, Sanchis-Segura, Leonardi-Essmann, Schneider, & Spanagel, 2010), suggesting *Per2* is involved in the sensitivity to the behavioral effects of morphine.

Chronic methamphetamine treatment enhanced the amplitude of locomotor rhythms and desynchronized the activity rhythm from the light–dark (LD) cycle, which was correlated with desynchronized expression of circadian genes between the striatum and SCN (Honma & Honma, 2009). In arrhythmic animals, regardless of the perturbation (i.e., SCN lesion, constant light [LL], or mutant and knockout), methamphetamine restores locomotor rhythmicity (Honma, Honma, & Hiroshige, 1986), suggesting the mechanisms that underlie methamphetamine-restored rhythmicity are substantially different from that of the molecular clock in other brain regions or tissues and completely independent from the SCN (Mohawk, Baer, & Menaker, 2009). It is unknown whether circadian gene mutations have any effects on methamphetamine-induced locomotor sensitization, reward, or withdrawal, but studies using other psychostimulants, such as cocaine, would suggest so.

Human Chronotypes, Circadian Genes, and Reward Neurocircuitry

In humans, defining the role of the circadian system in addiction is complicated, and reliably measuring robust markers of circadian phase and chronotype is particularly critical. Objective measures of circadian phase or entrainment typically rely on self-report, rather than objective biological measures. Sleep–wake preferences are often assessed by questionnaires that use subjective ratings of hypothetical situations, comparisons to the habits of others, and feelings of "best rhythm" (Roenneberg, Wirz-Justice, & Merrow, 2003). Participants are typically dichotomously categorized into either "morningness" (larks), or "eveningness" (owls) preferring (Horne & Ostberg, 1976). Morning chronotypes prefer daytime activity, with peak performance and alertness associated with morning hours, whereas evening chronotypes prefer the opposite. These approaches are evolving in order to become closer to the underlying biology (Roenneberg et al., 2003). There are a few studies showing a genetic basis for human chronotypes. For example, polymorphisms in *Clock* (3111T/C) are associated with eveningness (Katzenberg et al., 1998), and polymorphisms in *Per1* (2424T/C), *Per2* (111C/G), and *Per3* (647G) are associated with morningness (Carpen, Archer, Skene, Smits, & von Schantz, 2005; Carpen, von Schantz, Smits, Skene, & Archer, 2006; Johansson et al., 2003) among cohorts from different ethnic backgrounds. Several of these polymorphisms are also related to major depression, bipolar disorder, and addiction disorders (Kennaway, 2010; McClung, 2007c; Soria et al., 2010; Wang et al., 2012). The interpretation of these genetic findings remains difficult because chronotype is a complex polygenic trait (Duffy, Dijk, Hall, & Czeisler, 1999; Vink, Groot, Kerkhof, & Boomsma, 2001), and more advanced genetics analyses have the potential to cope with these issues and even reveal novel genes underlying these interactions (McCarthy et al., 2012).

Emerging evidence indicates there are shared genetic and biological factors between chronotype, mood disorders, and addiction. Chronotype is linked to affective disturbances (Hasler, Allen, Sbarra, Bootzin, & Bernert, 2010; Mansour, Monk, & Nimgaonkar, 2005), and reward circuitry is critical to the pathophysiology of mood disorders (Forbes et al., 2009; Nestler & Carlezon, 2006). In bipolar patients, evening preference is more prevalent, especially in those who experience rapid mood swings (Ahn et al., 2008; Hätönen, Forsblom, Kieseppa, Lonnqvist, & Partonen, 2008). Clinically depressed individuals who are also evening chronotypes display delayed and blunted positive affect rhythms (Boivin et al., 1997; Murray et al., 2009) and report poorer emotional adjustment and elevated rates of substance abuse (Giannotti, Cortesi, Sebastiani, & Ottaviano, 2002). Chronotype, circadian gene polymorphisms, and brain reward circuitry appear to be related. Using positron emission tomography, Hasler and colleagues measured diurnal variations of the rate of glucose uptake within brain regions associated with positive affect and reward in patients with insomnia who are either morning or evening types (Hasler, Dahl, et al., 2012). When compared with morning types, evening chronotypes exhibited a delayed and reduced diurnal peak of positive affect that correlated with a dampened morning-to-evening variation of glucose uptake in both the medial prefrontal cortex (mPFC) and the striatum (Hasler, Dahl, et al., 2012), supporting the notion that altered diurnal variation of mood- and reward-related brain circuitry function underlies the differences in positive affect between chronotypes. Circadian gene polymorphisms also mediate the correlation between decreased mPFC activity and reward. Healthy adolescents carrying a specific G allele (*Per2* SNP rs2304672) were more likely to display reduced activity in the mPFC during a reward task (Forbes et al., 2012). In response to reward outcome, mPFC activation was strongly negatively correlated with ventral striatal response in carriers of the G allele (Forbes et al., 2012). Moreover, later sleep midpoints were associated with reduced mPFC activity, but not *Per2* polymorphisms (Forbes et al., 2012). Thus, chronotype and circadian genes may mediate cortico-striatal activation following a rewarding stimulus (Haber & Knutson, 2010; Hasler & Clark, 2013). Future studies will require systematic and objective measurement of circadian phase, sleep–wake cycles, and environmental factors to determine the extent to which circadian and/or sleep homeostatic processes affect reward circuitry activation. It will also be important to identify robust biological markers of circadian phase, which could be used to more appropriately characterize diurnal variations in reward circuitry activation and mood.

Circadian Control of Brain Reward Mechanisms

The molecular components of the circadian clock are expressed in the mesocorticolimbic system central to reward processing and susceptibility to drugs of abuse (Panda et al., 2002; Rosenwasser, 2010). Consequently, these nuclei exhibit circadian patterns of activity in neuronal firing and neurochemical transcription and

release in mice and rats (McClung, 2007b), suggesting functional regulation of the circadian system over these processes. Additionally, many behaviors regulated by the limbic system, including drug-seeking behavior and locomotor sensitization, exhibit rhythmic patterns despite no change in the metabolic rates of the drugs themselves. Collectively, these phenomena point to a direct connection between circadian gene expression and reward, leading to the possibility that disruptions in the circadian system may directly affect risk for drug dependence and addiction.

The VTA

In the VTA, a number of processes associated with DA transmission are controlled by circadian genes and express diurnal rhythms. The expression of tyrosine hydroxylase (TH), the rate-limiting enzyme in DA synthesis, exhibits diurnal rhythms in both mice and rats (McClung et al., 2005; Webb, Baltazar, Lehman, & Coolen, 2009). Additionally, the expression of DA receptors and monoamine oxidase (MAOA) the primary enzyme responsible for DA degradation express diurnal rhythms (Hampp et al., 2008; McClung et al., 2005; Wirz-Justice, 1987). The canonical E-Box sites (CACGTG) present in *Maoa*, *Drd1/Drd2*, and *TH* genes suggest these are direct clock-controlled genes (CCGs) allowing for transcriptional control of these genes by core circadian proteins. Indeed, chromatin immunoprecipitation (ChIP) studies reveal that CLOCK and BMAL bind the E-box promoters of *TH* and *Maoa* and regulate their transcription (Hampp et al., 2008; Sleipness et al., 2007b). Despite their heterogeneous mechanisms of action, all drugs of abuse impinge upon the brain's reward circuitry, the majority of which increase DA concentrations in VTA projection sites, as well as within the VTA itself (Robison & Nestler, 2011). Disruptions in any of the myriad regulatory mechanisms that regulate baseline DA in the VTA increase the vulnerability to the rewarding properties of drugs. Therefore, it is not surprising that the behavioral aberrations associated with clock gene mutations in the context of reward are also associated with disruptions in DA transmission within the VTA or its primary projection sites. *Clock*Δ19 mice exhibit increased *TH* mRNA expression, higher DA firing, and increased bursting activity in the VTA (Coque et al., 2011; McClung et al., 2005; Figure 1). CLOCK-specific short hairpin RNA delivered locally into the VTA recapitulates these findings (Mukherjee et al., 2010), suggesting that CLOCK is potentially exerting its effects on DA transmission locally. The increase in *TH*, in *Clock*Δ19 mice suggests that the WT CLOCK protein acts as a modulator of DA

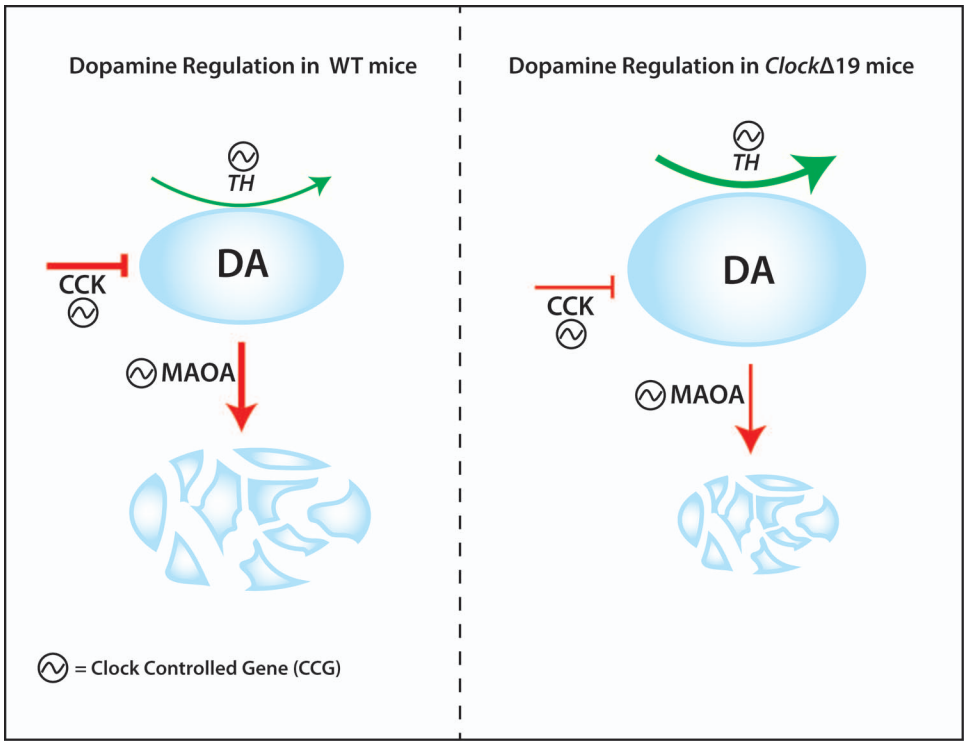

Figure 1. Proposed regulatory mechanisms of dopamine by circadian genes that contribute to the hyperdopaminergic phenotype of *clock* mutant mice. (Left) The synthesis of dopamine is controlled by the rate-limiting enzyme, tyrosine hydroxylase (TH), inhibited through the regulatory peptide, cholecystokinin (CCK), and degraded by the enzyme monoamine oxidase (MAOA). Collectively, these regulatory processes, which are all controlled by circadian clock genes, augment baseline dopamine signaling in VTA cell bodies and terminals in the NAc (Right). In *Clock*Δ19 mice, DA synthesis is heightened through an increase in *TH* mRNA, and disinhibited by a decrease in *cck* mRNA. Additionally, DA degradation is attenuated in NAc synapses via the downregulation of *mao-a* transcription. Collectively, these disruptions contribute to the increased reward-seeking behaviors in these mice.

synthesis, providing a potential mechanistic insight into the circadian control of reward. The role of CLOCK as an inhibitor of *TH* transcription is compelling, given the predominantly activational role of CLOCK in the CNS and periphery. The proximity of the E-box in the TH promoter to adjacent CRE sites may underlie the interference of the CLOCK protein for other transactivational targets (Manev & Uz, 2006). In addition to TH, other circadian-controlled transcriptional targets within the VTA may regulate DA output. Cholecystokinin (CCK), a neuropeptide colocalized with NAc-projecting DA neurons in the VTA (Hökfelt et al., 1980; Lança, De Cabo, Arifuzzaman, & Vaccarino, 1998), negatively modulates dopaminergic transmission in vivo (Hökfelt et al., 1980; Schade et al., 1995). CCK expresses an E-box in the promoter and is positively regulated by the CLOCK protein (Hansen, 2001).

Additionally, *Cck* mRNA is significantly downregulated in *Clock*Δ19 mice, and the behavioral phenotype of these mice can be recapitulated by VTA-specific knockdown of *Cck* (Arey et al., 2013). These results implicate *Cck* as a critical CCG that regulates DA output and contributes to reward-related behavioral outcomes. Most neurons in the VTA are dopaminergic or GABAergic (γ-aminobutyric acid) interneurons that exert local inhibitory control over DA output signals. In *Clock*Δ*19* mice, or following CLOCK RNA interference (RNAi) in the VTA, a number of GABAergic-associated genes are downregulated (Arey et al., 2013; McClung et al., 2005; Mukherjee et al., 2010), suggesting the potential loss of inhibitory control contributes to the increase in DA and associated hyperhedonia in these mice. Future studies examining the role of circadian genes on regulating GABAergic transmission in the VTA are necessary to determine if the loss of GABAergic control contributes to the molecular and behavioral phenotype of *Clock* mutants.

The NAc

The mechanisms by which drugs of abuse impinge upon the NAc and regulate reward and drug dependence are complicated by the cellular and molecular heterogeneity of this nucleus. Glutamatergic input from multiple regions, including the PFC and amygdala, and dopaminergic input from the VTA converge on subsets of neurons within the accumbens and potentially regulate different components of reward and motivation (Robison & Nestler, 2011). Although 95% of NAc neurons are medium spiny neurons, they differ in the expression profiles of DA D1- or D2-type receptors, and the net effect of drugs of abuse in this nucleus greatly depends on the specific receptor expression profiles and afferent networks involved. Many of these critical components are additionally regulated by circadian transcriptional mechanisms that modulate the response to drugs of abuse. Daily rhythms in DA release in the NAc, as measured by microdialysis (Schade et al., 1995), reveal circadian influence, although these rhythms may be the result of signaling from afferent networks. For example, *Clock* RNAi delivered into the VTA results in a net increase of DA release in the accumbens (Mukherjee et al., 2010), and TH and dopamine active transporter (DAT) rhythms in the NAc are abolished following SCN lesions (Sleipness et al., 2007b). However, in addition to afferent regulation, circadian genes within the accumbens likely regulate local dopaminergic tone. In *Per2* mutant mice, *Maoa* expression is lower in the accumbens, and DA levels are elevated in these mice compared with WT littermates (Hampp & Albrecht, 2008). Given that *Maoa* is a CCG, the elevation in DA directly connects a circadian mutation to disrupted DA metabolism, which likely contributes to the aberrant behavioral mutant phenotype (see above). The ratio of D1 to D2 in *Per2* mice is significantly decreased, which may be the result of compensatory processes to the elevated DA tone in the NAc (Hampp & Albrecht, 2008). This effect suggests that disruptions in the circadian system will affect multiple downstream processes in addition to the direct impact on CCGs. In *Clock*Δ19 mice, total DA levels in NAc are elevated, although this may be the result of increased firing and bursting of VTA-originating DA neurons that terminate in the NAc (Coque et al., 2011). Potentially, as a result of the increase in DA tone in the NAc of these mice, there is a dramatic decrease in the D1:D2 ratio, specifically due to a robust upregulation in D2 receptor expression (Spencer et al., 2012). Consequently, the locomotor response to a D1 agonist is blunted in *Clock*Δ19 mice, despite their normal locomotor response to cocaine. Conversely, the response to a D2 agonist is increased in these mice, which reflects the D1/D2 shift and a potential compensatory shift in DRD2 expression as a result of the inability of the mutant CLOCK protein to modulate DA transcription and release. As with *Per2* mice, further studies will be necessary to determine the relative impact of local clock gene regulation versus afferent signaling in contributing to the hyperhedonic phenotype in *Clock*Δ19 mice.

The SCN

In addition to the local regulation of mesolimbic circuitry by circadian genes, the rhythmic expression of DA and glutamate in these regions may be controlled at the circuit level through indirect connections originating in the SCN. Indeed, the SCN sends multisynaptic projections to the VTA through the medial preoptic area (mPOA; Cheng, Leslie, & Zhou, 2006; Jhou, Fields, Baxter, Saper, & Holland, 2009; Luo & Aston-Jones, 2009), providing an anatomical connection between the central pacemaker and rhythmic neurobiological processes in the VTA (see below). Lesions to the SCN in rats have an antidepressant effect, suggesting the master clock may exert control over mood and affect through connections to limbic circuits (Tataroglu, Aksoy, Yilmaz, & Canbeyli, 2004). Additionally, the efficacy of the "antidepressant" drug, agomelatine, a melatonin receptor agonist and a serotonin (5-HT_{2C}) antagonist, on social defeat-induced anxiety requires an intact SCN in rats (Tuma, Strubbe, Mocaer, & Koolhaas, 2005), pointing to a direct role of this nucleus in mediating the response to stress and anxiety.

More studies are needed to determine if SCN lesions affect reward and drug taking, although the indirect projections to limbic circuitry reveals functional control of the master clock over nuclei associated with reward and motivation. For example, the discovery of novel, "wide-spike" VTA neurons that exhibit strong circadian rhythms in firing activity, with selective spiking during the active phase of the diurnal cycle, suggests entrainment by the master clock (Luo & Aston-Jones, 2009; Luo, Georges, & Aston-Jones, 2008). Given that neither *Per* nor *Clock* mRNA expression is rhythmic in in vitro preparations of VTA tissue (Abe et al., 2002), the regulation of circadian processes within the VTA in vivo may involve multisynaptic inputs from the SCN. The rhythms of both DAT and TH are attenuated in the NAc following SCN lesions in

rats, leading to constitutively higher levels of both DAT and TH across the diurnal cycle (Sleipness et al., 2007b). This suggests that the SCN is exerting inhibitory control over DA rhythms in the NAc. However, it is possible that an extra-SCN oscillator is responsible for regulating circadian variation in specific drug-related behaviors (Sleipness, Sorg, & Jansen, 2007a).

In addition to neuronal control, the SCN may communicate with reward circuitry through humoral factors that are believed to contribute to motivation and affect (Figure 2). Prokineticin 2 (PK2) is a signaling molecule expressed in the SCN that is considered to be critical for the generation of circadian locomotor rhythms (Cheng et al., 2002). Intriguingly, all primary SCN targets express the PK2 receptor, including regions that project directly to the VTA, such as the lateral habenula and mPOA (Masumoto et al., 2006). PK2 knockout mice exhibit decreased anxiety and depression-like behaviors, which are rescued by intracerebroventricular infusions of PK2 (Li, Hu, & Zhou, 2009). These results provide further evidence of the influence of SCN signaling over mood and affect. Although the contribution of PK2 to reward- and drug-seeking requires further testing, these mice raise the intriguing possibility that SCN-derived neurochemicals can regulate limbic structures and associated behaviors.

The Effects of Drugs of Abuse on Circadian Rhythms and Circadian Genes in Humans and Animals

Chronic Drug Administration in Humans

Human drug addiction is linked to altered circadian rhythms, while circadian disruption, either by genetic mutation or environmental desynchrony, may be a risk factor for addiction, relapse, and withdrawal severity. Acute and chronic drug exposure alters molecular, physiological, and behavioral rhythms, which may involve SCN-dependent or SCN-independent (i.e., extra-SCN oscillators). Few human studies have examined the effects of drugs of abuse on molecular and physiological rhythms in tissues collected from addicted individuals. Peripheral blood mononuclear cells collected from human alcoholics immediately prior to hospital admission and 1 week into withdrawal showed a marked reduction in circadian gene expression compared with healthy controls (Huang et al., 2010). During the course of the withdrawal week, circadian gene expression tended to increase; however, these levels failed to approach that of controls and were not correlated with withdrawal severity (Huang et al., 2010). Skin fibroblasts collected from alcohol-dependent patients that were transfected with a *Per2*:luc construct to monitor real-time bioluminescence rhythms displayed rhythm amplitude and period similar to controls (McCarthy, Fernandes, Kranzler, Covault, & Welsh, 2013). However, within the alcohol-dependent cohort, period length was inversely correlated with illness severity, such that patients with a shorter period may be more severely alcohol dependent than those with longer periods (McCarthy et al., 2013). More extensive studies are necessary to determine whether these changes in molecular rhythms are robust across alcohol-dependent cohorts and/or if they vary depending on cell type, physiological state, and psychiatric subtype.

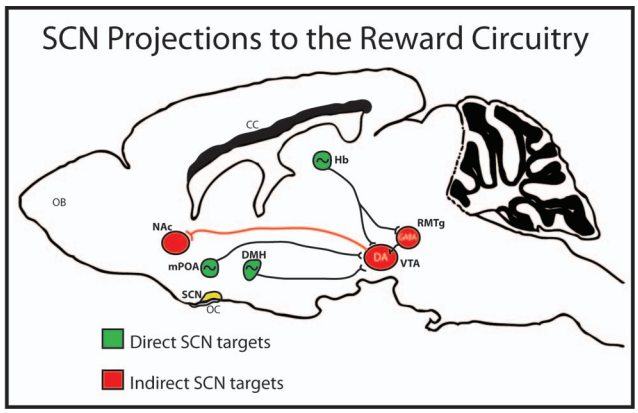

Figure 2. Indirect connections between the master clock and reward circuitry. The circadian control of reward and motivation may involve connections between the SCN reward circuitry. The SCN projects to three hypothalamic/epithalamic regions that directly project to the VTA, which in turn sends dopaminergic efferents to the NAc (red). These targets play significant roles in modulating reward- and drug-seeking behavior. The direct targets include the medial preoptic area (mPOA), dorsomedial hypothalamus (DMH), and lateral habenula (LHb), all of which express clock genes that may exert local circadian control of these processes. Direct SCN targets receive signals through monosynaptic afferents and/or diffusible signals (see text).

In chronically alcohol-drinking mice and rats, changes in circadian gene expression depend on alcohol paradigm, length and dose of alcohol exposure, and brain region or peripheral tissue. In rats, chronic ethanol liquid diet shifted the gene expression rhythms of *Per2* and *Per3* in the SCN and *Per1* and *Per2* in the arcuate nucleus (Chen et al., 2004), but minimally affected circadian gene expression in the SCN (Filiano et al., 2013). However, chronic alcohol drinking for extended periods (e.g., 6 to 12 months) reduced gene expression of arginine vasopressin (AVP), vasoactive-intestinal polypeptide (VIP), and somatostatin (SST) in the SCN and the number of SCN neurons expressing these neuropeptides, which persisted during withdrawal from alcohol (Madeira et al., 1997; Madeira & Paula-Barbosa, 1999). Both AVP and VIP are differentially distributed across the ventral (core) and dorsal (shell) SCN, respectively (Antle & Silver, 2005), which contributes to their distinct functional roles in the SCN (Aton, Colwell, Harmar, Waschek, & Herzog, 2005; Yan et al., 2007). Reductions of AVP and VIP signaling in the SCN provide a plausible mechanism by which chronic alcohol drinking or during alcohol withdrawal alters circadian responses to photic stimuli and circadian period (Logan, McCulley, Seggio, & Rosenwasser, 2012; Rosenwasser, Logan, & Fecteau, 2005; Seggio, Fixaris, Reed, Logan, & Rosenwasser, 2009; Seggio, Logan, & Rosenwasser, 2007).

Acute and chronic treatment of rodents with psychostimulants, opiates, and other drugs of abuse alter expression of circadian genes in the SCN and in reward- and stress-related brain regions. Acute and repeated methamphetamine injections in mice increases *Per1* and *Per2* expression in the SCN and alters the expression rhythms of *Per1, Per2, Bmal1,* and *Rev-erbα* in the striatum, which are both likely mediated by dopaminergic and glutamatergic signaling (Iijima, Nikaido, Akiyama, Moriya, & Shibata, 2002; Li et al., 2008; Nikaido, Akiyama, Moriya, & Shibata, 2001; Sanchis-Segura, Jancic, Jimenez-Minchan, & Barco, 2009; Webb et al., 2009; Wongchitrat, Mukda, Phansuwan-Pujito, & Govitrapong,

2013). Altered expression of circadian genes in the dorsal striatum and the NAc persist during acute and protracted withdrawal from methamphetamine and heroin. Repeated morphine administration stably enhances *Per1* and *Per2* expression in the frontal cortex and striatum (Ammon-Treiber & Hollt, 2005; Li et al., 2008). Inhibiting *Per1* activation in the frontal cortex, hippocampus, and striatum, prevents morphine CPP and activation of extracellular signal-related kinase (ERK) and cAMP-responsive element-binding protein (CREB) signaling pathways (Li et al., 2008), indicating this mechanism is important for morphine reward.

Chronic cocaine administration differentially affects circadian gene expression across many mood- and reward-related brain regions. In the hippocampus, chronic cocaine increased the expression of *Per1* and *Per2* and decreased the expression of *Bmal1* and *Cry1*, whereas in the caudate putamen, only *Per1* and *Clock* were increased (Uz et al., 2005). Also, *Per2*, *Cry1*, *Bmal1*, and *Clock* were increased in the dorsal striatum following chronic cocaine (Lynch, Girgenti, Breslin, Newton, & Taylor, 2008). We recently demonstrated that chronic, but not acute cocaine administration, increased the expression and altered the diurnal variation of the circadian transcription factor, *Npas2*, along with *Per1* and *Per3* expression in the NAc (Falcon, Ozburn, Mukherjee, Roybal, & McClung, 2013). Chronic cocaine also enhanced the binding of NPAS2 to both the *Per1* and *Per3* promoters in the NAc and dorsal striatum, but had no effect on CLOCK binding or the expression of *Clock* and *Bmal1* (Falcon et al., 2013). Overall, these results suggest that in response to chronic cocaine, CLOCK and NPAS2 may be differentially regulated depending on the brain region and signaling mechanism.

There is extensive crosstalk between the molecular clock and dopaminergic pathways. For example, the circadian variation of the locomotor response to a D2/D3 receptor agonist correlates with the peak (day) and trough (night) of D2:D3 receptor ratios in the striatum (Akhisaroglu et al., 2005). Furthermore, activation of D2/D3 receptors in the mouse striatum inhibits *Clock* and *Per1* expression, whereas D1 receptor activation stimulates *Npas2*, *Clock*, *Bmal1*, and *Per1* expression (Imbesi et al., 2009). However, there is very little known about the downstream molecular mechanisms that are affected by changes in circadian gene expression following chronic drug administration and whether these changes lead to brain region-specific alterations or plasticity that plays a role in the addiction process.

The master circadian pacemaker of the SCN is also vulnerable to drugs of abuse. Drugs of abuse directly affect neuronal firing within the SCN and modulate afferent and efferent pathways for photic and nonphotic entrainment. Ethanol treatment blocks glutamate-induced phase delays of SCN firing, whereas cotreatment with ethanol and 8-OH-DPAT ($5HT_{1A}R$ agonist) enhances phase advances of SCN firing (McElroy, Zakaria, Glass, & Prosser, 2009; Prosser & Glass, 2009). Ethanol also disrupts circadian phase resetting and alters the period (Brager, Ruby, Prosser, & Glass, 2010, 2011; Seggio et al., 2007). Other drugs of abuse, including methamphetamine, cannabinoids, nicotine, and cocaine, alter the pattern and rate of SCN firing (Acuna-Goycolea, Obrietan, & van den Pol, 2010; Biello & Dafters, 2001; Yang, Wang, Cheng, Kuo, & Huang, 2010). Nicotine phase advances SCN firing rhythms during the subjective night, presumably through activation of M1 and M4 acetylcholine receptors (Liu & Gillette, 1996; Yang et al., 2010). Circadian variation of behavioral sensitivity to nicotine may involve SCN-dependent (e.g., melatonin) or -independent (e.g., mesolimbic DA) mechanisms (Ferguson, Kennaway, & Moyer, 1999; Pietilä, Laakso, & Ahtee, 1995). Cocaine also affects normal SCN functioning. An acute cocaine injection directly into the SCN induces large phase advances during the midsubjective day, which can be prevented using a serotonin receptor antagonist, and attenuates photic phase delays during the early subjective night (Brager et al., 2011).

Most of the aforementioned studies address the acute effects of drug administration on SCN functioning. There is very little known about the effects of repeated administration or withdrawal from drugs of abuse on SCN functioning. A few recent studies suggest that the SCN develops rapid tolerance to acute drug effects that potentially underlies the consequences of chronic drug use on circadian rhythms. Indeed, pretreating the SCN with either ethanol or methamphetamine prevents glutamate- and serotonin-induced phase shifts in neuronal firing (Biello & Dafters, 2001; Ruby, Prosser, DePaul, Roberts, & Glass, 2009), indicating the SCN may develop rapid tolerance to acute drug exposure. Although withdrawal from chronic drug administration produces long-lasting changes to SCN firing, suggesting chronic drug-induced plasticity in the SCN (Cutler, Mundey, & Mason, 1999). Following chronic intermittent ethanol vapor exposure, C3H/HeJ, but not C57BL/6J, mice display a significantly shortened period of running wheel activity rhythms, a behavioral output of SCN-driven rhythms (Logan et al., 2012). Thus, there are complex genetic factors underlying the acute and chronic effects of drugs of abuse on SCN functioning and overt behavioral rhythms. Future studies will need to expand on previous work in order to identify the mechanisms underlying rapid drug tolerance in the SCN, the circadian effects of acute and chronic drug exposure, and whether these changes directly or indirectly affect SCN outputs.

Developmental Exposure to Drugs of Abuse

During the prenatal period, exposure to drugs of abuse has a deleterious impact on fetal development that consequently enhances the risk for the emergence of diseases later in life, including psychiatric diseases, such as depression and anxiety (Behnke, Smith, & Committee on Substance Abuse, & Committee on Fetus & Newborn, 2013; Molteno, Jacobson, Carter, Dodge, & Jacobson, 2014; O'Connor & Kasari, 2000; Pei, Denys, Hughes, & Rasmussen, 2011; Streissguth et al., 2004; Treit et al., 2013). A clinical diagnosis of depression or anxiety is often preceded by motor, cognitive, sleep, and behavioral problems in early childhood and adolescence (Kelly, Day, & Streissguth, 2000; Logan, Brown, & Hayes, 2013; Nanson & Hiscock, 1990; Streissguth et al., 2004). These behavioral issues, including attention and social deficits, impulsivity, hyperactivity, and anxiety, may be associated with stress hyperresponsiveness and circadian disruptions (Gruber, Sadeh, & Raviv, 2000; McClung, 2013; Sher, 2003; Verma, Hellemans, Choi, Yu, & Weinberg, 2010). A few lines of evidence support a link between prenatal drug exposure and an increased risk for substance abuse later in life (Alati et al., 2006; Baer, Barr, Bookstein, Sampson, & Streissguth, 1998). For example, disturbances in sleep–wake patterns and stress responsiveness are often observed in children with fetal alcohol spectrum disorder, who are at an increased risk for alcohol abuse during adulthood (Alati et al., 2006; Chen, Olson, Picciano, Starr, & Owens, 2012; Troese et al.,

2008; Verma et al., 2010). In humans, very little is known about the structural and functional effects of prenatal drug exposure on circadian physiology and behaviors and their possible contribution to the risk of developing certain diseases. A majority of the evidence showing the circadian system is particularly malleable when exposed to drugs of abuse during early development stems from animal studies.

Animal models of developmental alcohol exposure indicate that the circadian system is particularly vulnerable to alcohol. In rats, developmental alcohol exposure during the human "equivalent" of the last trimester (i.e., postnatal Days 4–9) alters circadian responses to light-induced phase shifts, entrainment, and reentrainment, and shortens the free-running period during constant conditions (Allen et al., 2005a; Allen, West, Chen, & Earnest, 2005b; Farnell, West, Chen, Allen, & Earnest, 2004; Sakata-Haga et al., 2006). Similarly, adult flies reared on ethanol-containing solutions during the third larval instar stage display significantly shortened free-running periods (Seggio, Possidente, & Ahmad, 2012). The degree of period shortening depends on the dose of ethanol, such that the highest dose (20%) results in the shortest period (Seggio et al., 2012). The shortened free-running period in adult rats and flies exposed to alcohol during development suggests there are similar molecular mechanisms underlying these seemingly permanent alterations to the circadian system.

Prenatal alcohol exposure also affects the development of functional components of the circadian system, such as the retina (Chmielewski et al., 1997; Tenkova, Young, Dikranian, Labruyere, & Olney, 2003), optic tracts (Parson & Sojitra, 1995), and dorsal and medial raphe nuclei (Sari & Zhou, 2004; Sliwowska, Song, Bodnar, & Weinberg, 2014). In the SCN, the structural effects of alcohol exposure during development appear to be minimal. Alcohol exposure during postnatal Days 4–9 in rats reduces SCN neuronal density, without affecting cell number or volume (Farnell et al., 2004). Loss of myelinated optic axons or raphe neurons and reduced neuronal density in the SCN may alter circadian entrainment under entrained conditions and reentrainment following a light pulse.

In addition to structural changes, there is growing evidence that developmental alcohol exposure targets components of the molecular clock and other signaling neuropeptides involved in circadian functions. In the SCN of adult rats exposed to alcohol during postnatal Days 4–9, the expression and rhythm amplitude of the neurotrophin, brain-derived neurotrophic factor (BDNF), was significantly reduced. BDNF modulates the activation of NMDA glutamate receptors located in the SCN and on terminals from the retinohypothalamic tract, which mediates the circadian response to photic phase resetting and photic phase shifting (Kim, Choi, & Colwell, 2006; Liang, Allen, & Earnest, 2000). It is likely that BDNF, in part, contributes to the altered phase resetting of animals exposed to alcohol during development.

Developmental alcohol exposure affects the expression of circadian genes in the hypothalamus and other brain regions. Recent evidence suggests a primary role of the *Per* genes in circadian and stress phenotypes associated with developmental alcohol exposure. In the SCN, developmental alcohol exposure reduced the amplitude of the *Per2* and *Cry1* expression rhythms and enhanced the amplitude of *Per1* and *Bmal1* (Farnell et al., 2008). Less dramatic changes in expression rhythms were found in the cerebellum (Farnell et al., 2008). A recent study by Seggio and colleagues revealed that period effects of developmental alcohol exposure depend on the inherent circadian period and correlate with changes in *Per2* expression (Ahmad, Steinmetz, Bussey, Possidente, & Seggio, 2013). In another study, mutant flies that displayed either a shortened (Per2S) or a lengthened (Per2L) activity period were reared in an ethanol-containing solution. Developmental alcohol exposure shortened and lengthened the periods of Per2L and Per2S mutant flies, respectively, while decreasing *Per2* in Per2L flies and increasing *Per2* in Per2S flies (Ahmad et al., 2013), suggesting *Per2*, in particular, may be a primary target for alcohol to permanently affect the circadian system. In the mediobasal hypothalamus, the overall expression levels and rhythm amplitudes of *Per1* and *Per2* were significantly reduced in animals exposed to alcohol during early development (Agapito, Barreira, Logan, & Sarkar, 2013; Chen, Kuhn, Advis, & Sarkar, 2006). The lack of *Per2* reduced the stimulatory response of ethanol on hypothalamic genes and neuropeptides involved in metabolism and stress regulation (Agapito et al., 2010). Developmental alcohol exposure may alter *Per2* expression and subsequent downstream pathways by a number of molecular mechanisms, such as accelerating degradation by CK1ε and epigenetic modifications.

Most likely, other drugs of abuse affect the development of the circadian system. Cocaine exposure during development reduces the response to a light pulse during the early subjective night (Strother, Vorhees, & Lehman, 1998), and alters the expression of circadian genes *Per3* and *Bmal1* (Shang & Zhdanova, 2007). The effects of cocaine on the development of the circadian system likely involve Drd1 receptors. Prenatal administration of Drd1 agonists, including cocaine, activate *c-fos* expression in the fetal SCN (Ferguson, Rowe, Krupa, & Kennaway, 2000; Weaver, Rivkees, & Reppert, 1992) and alter the response to light closely following birth and in adulthood (Ferguson & Kennaway, 2000; Ferguson et al., 2000; Strother et al., 1998). Other stimulants, such as caffeine and nicotine, induce *c-Fos* in the fetal SCN, although distinct neurotransmitter mechanisms are involved in entraining the fetal SCN (Shearman & Weaver, 2001). The impact of drugs of abuse on the developmental trajectory of the fetal circadian system may have profound health consequences (Brooks & Canal, 2013). Future studies will need to determine the extent to which the development of the circadian system is involved in the emergence, progression, and comorbidity of psychiatric diseases, such as anxiety, depression, and addiction, across the life span.

Genetic Linkages Between Circadian and Alcohol Phenotypes

Shared genetic linkages between the circadian clock and alcohol-related behaviors are suggested by studies showing that rats and mice selectively bred for alcohol preference, withdrawal, and behavioral responses to acute alcohol, exhibit different circadian phenotypes. In high and low alcohol-preferring mice (HAP-1 and LAP-1, respectively), HAP-1 mice have shorter circadian periods in constant darkness (DD) than LAP-1 mice (Hofstetter, Grahame, & Mayeda, 2003). Other high drinking mouse lines, such as the High Drinking in the Dark (HDID-1 and −2), (Crabbe et al., 2009; Crabbe, Spence, Brown, & Metten, 2011; Rhodes, Best, Belknap, Finn, & Crabbe, 2005), display shorter free-running periods and less coherent activity rhythms in LL relative to the genetically heterogeneous progenitor line (Hs/Npt) controls (Mc-

Culley, Ascheid, Crabbe, & Rosenwasser, 2013). In selectively bred rat lines for high and low alcohol drinking, high preferring (P) and high alcohol drinking (HAD-2) rats have shorter circadian periods in LL and DD, respectively, than their low drinking counterparts nonpreferring (NP) and low alcohol drinking (LAD-2) rats (Rosenwasser, Fecteau, et al., 2005). Moreover, under gradually shortening LD cycles, NP rats are more readily able to entrain to changing LD cycles than P rats (Rosenwasser, Fecteau, et al., 2005).

Selective breeding for alcohol withdrawal severity also influences circadian phenotype. The Withdrawal Seizure Prone (WSP-1 and −2) and Withdrawal Seizure-Resistant (WSR-1 and −2) mice were selected for high and low handling-induced convulsions during alcohol vapor withdrawal (Crabbe & Phillips, 1993; Kosobud & Crabbe, 1986). In DD, WSP-2 mice have longer circadian periods than the WSR-2 mice (McCulley et al., 2013). Overall it appears that selective breeding for alcohol drinking or other alcohol traits seems to alter responsiveness to light, such as in the case of the P rats, or disrupt the innate circadian period, as in the case of the HAP-1 mice and the HAD-2 rats. Similar mechanisms could be involved in the withdrawal-resistant and -prone mice. The high-drinking P and HAD-2 rats are derived from distinct progenitor stocks and genetic backgrounds and exhibit different circadian phenotypes in DD and LL, yet identifying the genetic loci underlying these phenotypes is difficult because of the inherent polygenic complexity of both circadian and alcohol phenotypes (Crabbe, Phillips, Buck, Cunningham, & Belknap, 1999; McCulley et al., 2013; Shimomura et al., 2001).

A few studies have pointed toward GABAergic neurotransmission as a potential common mechanism underlying circadian and alcohol-related phenotypes. In the SCN, the molecular clock regulates GABAergic neurotransmission, which is important for coordinated neuronal firing (Belenky, Yarom, & Pickard, 2008; Freeman, Krock, Aton, Thaben, & Herzog, 2013; Moore & Speh, 1993). Both GABA-mediated neurotransmission and GABA-A receptors are also important for many alcohol-related behaviors (Buck & Finn, 2001; Lovinger, 2008; Sprow & Thiele, 2012). For example, quantitative trait locus (QTL) mapping studies in WSP and WSR mice and recent gene coexpression analyses in HDID mice, strongly suggest the role of GABA-A receptors in their selected phenotypes (Bergeson et al., 2003; Buck & Finn, 2001; Iancu et al., 2013). As addressed above, most of the selectively bred mouse lines for alcohol-related phenotypes display divergent circadian behavioral phenotypes. New genetic tools and analyses will help identify interactions between the GABAergic system and the molecular clock. Using high-throughput genome sequencing, or other array based approaches, in selectively bred lines, researchers can now construct gene networks that could help to identify the mechanisms at the intersection of circadian and alcohol phenotypes.

Circadian Photoperiod, Environmental Desynchrony, and Drug-Related Behavior

Circadian photoperiod and desynchrony affects drug administration and responses. Experimental manipulation of the day length and chronic shifting of the LD cycle (shift-lag) can increase or decrease drug-related behaviors depending on the paradigm, species, and behavior. In HAD-1 rats, repeated 6-hr LD phase advances at 3- to 4-week intervals decreases alcohol drinking in males and increases drinking in females (Clark, Fixaris, Belanger, & Rosenwasser, 2007). A similar paradigm reduces alcohol drinking in male and female Fischer and Lewis rats (Rosenwasser, Clark, Fixaris, Belanger, & Foster, 2010), but increases voluntary consumption in Spraque-Dawley rats (Gauvin et al., 1997). Photoperiod changes (i.e., day length) and chronic shifting paradigms have little effect on alcohol intake in mice, although both DD and LL reduce voluntary consumption in mice and hamsters (Rosenwasser & Fixaris, 2013; Trujillo, Do, Grahame, Roberts, & Gorman, 2011). Cocaine reinstatement is also unresponsive to long days in rats; however, shorter photoperiods profoundly suppress cocaine reinstatement, and this persists even after the animals are transferred back to a standard 12:12 LD cycle (Sorg, Stark, Sergeeva, & Jansen, 2011). It will be important to elucidate how changes in photoperiod alter reward circuit function and drug-induced plasticity and to clarify whether these effects are SCN dependent.

Changes in day length (e.g., short vs. long days) and phase of light onset (i.e., shifting paradigms) activates glucocorticoid release and receptor expression in the brain and peripheral tissues, which is thought to aid in the resetting and adjustment of the circadian system to the environment (Gibson, Wang, Tjho, Khattar, & Kriegsfeld, 2010; Kiessling, Eichele, & Oster, 2010; Pezük et al., 2012). Circadian glucocorticoid oscillations in the brain have a role in neuroplasticity (Liston et al., 2013) and modulate the functional output of regions downstream from the SCN (Segall & Amir, 2010). Indeed, TH and DAT in the mPFC and dorsal striatum respond to changes in photoperiod, but not in the NAc or the VTA (Sorg et al., 2011). A recent study demonstrated that photoperiod mediates anxiety- and depression-like behavior by directly mediating DA signaling in the hypothalamus. Interestingly, a short day photoperiod (which is less stressful for a nocturnal mouse) increased the number of dopaminergic neurons in the periventricular (PeVN) and paraventricular (PVN) hypothalamic nuclei (Dulcis, Jamshidi, Leutgeb, & Spitzer, 2013). In response to long day photoperiods (a more stressful situation), a subset of hypothalamic neurons actually "switched" their neurotransmitter production from primarily DA to SST (Dulcis et al., 2013). Both dopaminergic and SST interneurons synapse onto PeVN corticotropin-releasing factor (CRF) neurons (Kumar, 2007), which may regulate stress-induced psychiatric diseases. The decrease in the number of dopaminergic neurons following a long day photoperiod reduced the density of D2 receptors on CRF-containing terminals (Dulcis et al., 2013). Reduced postsynaptic density of D2 receptors on CRF neurons dramatically elevated CRF levels in the CSF following a long day photoperiod (Dulcis et al., 2013). The opposite was found following a short day photoperiod, indicating a bidirectional photoperiodic modulation of neurotransmitter switching in the hypothalamus that regulates CRF response and behavior. Indeed, a short day photoperiod decreased anxiety- and depression-related behaviors, whereas a long day photoperiod had the opposite behavioral effect (Dulcis et al., 2013). The behavioral effects of a long day photoperiod seemed to be mediated directly by dopaminergic signaling, as dopaminergic lesions in the hypothalamus similarly increased anxiety- and depression-like behavior (Dulcis et al., 2013), and quite strikingly, the behavioral effects of dopaminergic lesions were partly reversed by the reemergence of dopaminergic neurons

following a short day photoperiod (Dulcis et al., 2013). The ability of a short day photoperiod to reverse the behavioral effect of dopaminergic lesions was blocked by the administration of D1 and D2 antagonists (Dulcis et al., 2013). For the first time, these results provide a mechanism by which photoperiod modulates behavior that may contribute to mood and addiction disorders (LeGates et al., 2012). These studies provide novel insights into how changes in day length or environmental desynchrony potentially modulate drug taking and response.

Circadian Rhythms of Drug Self-Administration: Animal Models of "Loss of Control"

Drug self-administration follows a robust diurnal pattern in humans and animals. Voluntary alcohol consumption and cocaine self-administration in nocturnal rodents is primarily consolidated into the dark phase (active), with peaks typically occurring during the early night (Aalto & Kiianmaa, 1987; Agabio et al., 1996; Boyle, Smith, & Amit, 1997; Dole, Ho, & Gentry, 1985; Lynch & Taylor, 2004; Pasley, Powell, & Halberg, 1987; Roberts, Brebner, Vincler, & Lynch, 2002; Trujillo, Roberts, & Gorman, 2009). Cocaine self-administration also free-runs under constant conditions, indicating an endogenous oscillatory regulator of drug intake (Bass, Jansen, & Roberts, 2010). The circadian pattern of drug self-administration persists under constant conditions (Bass et al., 2010). In the general human population, alcohol consumption peaks during the early evening, whereas alcohol-dependent individuals report craving for their first drink peaks during the early morning (Danel, Jeanson, & Touitou, 2003), suggesting a temporal "shift" or loss of "normal" diurnal alcohol drinking. Thus, loss of normal circadian rhythm of drug-self-administration may be an informative marker for the transition from use to abuse to addiction.

The progression toward addiction is characterized by the transition from sporadic drug use to consistent drug taking, intense binging, and persistent drug seeking. A "loss of control" is the hallmark of an addicted state. In animals, experimental paradigms where access to a drug is presented intermittently or continuously but separated by periods of deprivation over long periods of time (i.e., alcohol deprivation effect [ADE]) escalates drug seeking and drug taking (Hölter & Spanagel, 1999; Perreau-Lenz et al., 2012; Roberts et al., 2002; Sinclair & Senter, 1968; Tornatzky & Miczek, 2000). The few studies that have investigated the diurnal patterns of drug intake using these methods indicate alterations in the circadian pattern of drug self-administration. Extended continuous access to nicotine reduces the peak of self-administration during the night (active phase) and increases intake during the day (inactive phase; O'Dell et al., 2007). Daily cocaine intake is also increased in rats allowed to self-administer during controlled intermittent access trials (Lynch & Taylor, 2004). The circadian pattern of cocaine self-administration seems to depend on the dose and availability of the drug (Roberts et al., 2002). Increasing the allowable dose of cocaine during daily intermittent access eventually leads to a loss of the daily rhythmicity of self-administration (Roberts et al., 2002). In addition, ADE results in the complete loss of normal circadian rhythmicity of alcohol self-administration (Perreau-Lenz et al., 2012; Vengeliene, Noori, & Spanagel, 2013). These are the most impressive pieces of evidence suggesting that a loss of rhythmicity of drug self-administration may represent a loss of control. It will be important to determine whether chronotherapeutics and compounds that are known to target certain components of the molecular clock reduce drug self-administration by altering the circadian pattern of drug intake (Perreau-Lenz et al., 2012; Vengeliene et al., 2013).

Future Directions

The challenge of future research is to further tease apart the mechanisms by which the circadian system modulates affective and addictive phenotypes. For example, circadian genes may modulate behavior by classic circadian (i.e., SCN driven) or novel mechanisms. Certain behavioral phenotypes in circadian mutant mice may be "secondary" to alterations in circadian rhythms at the cellular or systems level, rather than the action of the circadian gene on an entity that is "independent" of the molecular clock (Rosenwasser, 2010). Studies using mice with global circadian gene mutations are somewhat incapable of reliably distinguishing between these two possible roles. However, it is important to consider that not all of the circadian mutations produce the same behavioral phenotypes, even if the mutation is expected to have similar roles in the molecular clock.

The use of site-specific disruption of circadian genes through RNAi or clock gene/protein rescue experiments in transgenic mice are useful methodologies in determining the local contribution that these genes play in regulating reward and susceptibility to drug administration. Additionally, studies investigating other clock genes or clock-controlled targets will be useful to determine the regulatory mechanisms by which individual circadian genes or circadian rhythmicity as a whole differentially regulate drug-related phenotypes. For example, *Clock* knockdown in the VTA of WT mice recapitulates both the mood- and drug-related behavior, but not the circadian phenotypes, of *Clock*Δ19 mice (Mukherjee et al., 2010; Ozburn et al., 2012, 2013). Similarly *Per1* and *Per2* knockdown in the NAc recapitulates the anxiety-like behaviors of $Per1^{-/-}$; $Per2^{-/-}$ mice (Spencer et al., 2013). Although these studies provide regional specificity for the action of a particular circadian gene, the question remains if these gene manipulations alter cellular rhythms that give rise to the behavioral phenotypes. Current studies are determining whether the behavioral phenotypes following circadian gene knockdown are due to loss of molecular clock function in the mesolimbic circuitry or whether these directly or indirectly regulate pathways that influence the central clock in the SCN.

Developing tools and techniques that allow for the spatial and temporal control of neural circuits will be critical for determining the site-specific influence of the circadian system over reward- and drug-seeking behaviors. Specifically, isolating the effects of circuit-level versus intranucleus disruptions of circadian rhythms and their impact on behavior will be greatly aided by the implementation of cutting-edge tools that are already contributing to our knowledge of reward and addiction. Our understanding of the mechanisms that control the intercellular communication within the SCN, which is critical for generating rhythmic output, has been greatly enhanced by the use of designer receptors exclusively activated by designer drugs (DREADDs). Brancaccio and colleagues utilized this technology as a mechanism to activate G-coupled pathways in the SCN and discovered that Gq-Ca^{+} signaling is required for the control of cellular rhythm coherence in

the SCN and is dependent on VIP signaling (Brancaccio, Maywood, Chesham, Loudon, & Hastings, 2013). The augmentation of clock gene signals through these peptidergic cues reveals extracircadian control over overt rhythms, which adds an additional layer of complexity connecting the network-related properties to circadian rhythmicity. Utilizing DREADDs to augment intercellular rhythms in distinct nuclei will provide novel insight into the mechanisms connecting cellular rhythms to network function in the context of reward. For example, desynchronized phase coupling in *Clock*Δ19 mice may be rescued through DREADD technology in order to determine the relative contribution in phase uncoupling to the manic behaviors in these mice. In addition to DREADDs, optogenetic technology may be used in the future to determine the contribution of SCN efferents to limbic structures in the regulation of reward circuitry. This technology has already uncovered many circuit level mechanisms that contribute to drug reward, motivation, and aversion (Stamatakis & Stuber, 2012).

The long-term adaptations to limbic circuits following acute exposure to drugs of abuse implicate transcriptional modifications as a mechanism of drug dependence. It has become clear that in addition to classic transcriptional factors, epigenetic modifications to DNA are critical regulatory processes that result in myriad behavioral adaptations to drug exposure (Renthal & Nestler, 2008). The ability of circadian genes to modify chromatin structure provides a compelling bridge between circadian genes and the underpinnings of motivation and reward. The discovery that the CLOCK protein exhibits histone acetyl transferase activity (Doi, Hirayama, & Sassone-Corsi, 2006) has greatly enhanced our understanding of the mechanisms by which circadian genes can regulate gene transcription. Given the potent ability of epigenetic modifiers to pharmacologically alter reward- and drug-seeking behaviors, the connection between circadian genes and chromatin state may reveal numerous therapeutic targets for treating drug dependence. For example, the histone deacetylase (HDAC) Sirtuin1 (SIRT1) is expressed in the NAc, where it significantly enhances the behavioral effects of cocaine in mice (Renthal et al., 2009). The enzymatic activity of SIRT1 requires the cofactor nicotinamide adenine dinucleotide (NAD^+), which is connected to the circadian machinery by the NAD rate-limiting enzyme NAMPT (Nakahata, Sahar, Astarita, Kaluzova, & Sassone-Corsi, 2009), a CCG. In turn, SIRT1 can directly affect clock gene expression, as BMAL1 and PER2 are themselves SIRT1 targets (Asher et al., 2008; Nakahata et al., 2008). The connection between the circadian system and epigenetic modifiers highlights the importance of examining mechanisms beyond classical E-Box control of transcription. Here, the direct regulation of an HDAC by the circadian system can itself affect the influence of drugs of abuse in the NAc and alter the adaptive response to drugs through noncanonical clock targets, in addition to the direct effects of circadian genes on CCGs. The circadian regulation of the epigenome yields highly dynamic changes in transcriptional access to DNA (Bellet, Orozco-Solis, Sahar, Eckel-Mahan, & Sassone-Corsi, 2011), which likely includes genes associated with reward and motivation. Modifications to this circadian epigenome, therefore, will likely yield differential responses to drugs of abuse, depending on permissiveness of the chromatin–DNA complex. Future studies exploring the relationship between circadian genes and the epigenome in limbic structures will undoubtedly advance our understanding of the connection between the circadian system and reward.

For over a decade, large-scale gene expression studies have identified circadian-regulated genes using microarrays in brain and peripheral tissues. More recently, newer high-throughput sequencing approaches have begun to construct more comprehensive perspectives on circadian regulation of tissue-specific signaling pathways (Eckel-Mahan et al., 2012; Hughes, Grant, Paquin, Qian, & Nitabach, 2012; Koike et al., 2012; Rey et al., 2011). These tools are poised to reveal novel connections between gene regulation and addiction (Hitzemann et al., 2013; Renthal & Nestler, 2008) and have already been used to study genome-wide transcriptional changes associated with chronic cocaine (Maze et al., 2011) and morphine treatments (Sun et al., 2012). Such a comprehensive and integrative approach has yet to be used in the mammalian brain within the context of circadian rhythms. For example, chromatin immunoprecipitation sequencing (ChIP) will help identify targets of circadian transcription factors in reward-related brain areas following acute and chronic drug treatments. There is very little known about how changes in circadian gene or protein expression alter downstream outputs that are involved in drug induced behaviors and neuroplasticity. Integrative approaches using transcriptome and proteome data collected from specific cell types or brain regions across circadian time or in connection with circadian proteins following acute and chronic drug exposure will surely determine the extent to which localized clocks are involved in drug-related neurocircuitry. To uncover the differential role of circadian genes in drug related behaviors, these approaches can be used with circadian mutant mice or cell- and region-specific, viral-mediated gene knockdown or overexpression. Systematic behavioral phenotyping in response to drugs of abuse of other circadian mutants besides the *Per* and *Clock* mutants, such as *Cry*, *Rev-erbα*, *Bmal1*, and *Fbxl3*, will also aid in this endeavor. Indeed, it was recently reported that *Afterhours* mice carrying a mutation in the circadian gene *Fbxl3* display a long circadian period (~27 h) and reduced anxiety- and depression-like behavior (Keers et al., 2012). Genome-wide analyses revealed an associated between a variant in *Fbxl3* and bipolar disorder (Keers et al., 2012).

Whole genome approaches such as deep-sequencing and proteomics are useful tools for identifying novel gene and protein regulatory networks that could be either modifiers of the molecular clock or outputs of the clock. Newly available genetically and phenotypically heterogeneous mouse populations, such as the Collaborative Cross (Threadgill & Churchill, 2012) and Diversity Outbred (Svenson et al., 2012), provide a valuable resource for mapping novel genomic loci to behaviors related to mood and addiction (Logan, Robledo, et al., 2013). High-density haplotype mapping and high-throughput genotyping are readily accessible tools for studying the genetics underlying inherent circadian and addiction phenotypes. Recently, in silico locus mapping, gene expression, and behavioral analyses identified *Per3* variants as a candidate gene for circadian-, stress-, and addiction-related phenotypes (Wang et al., 2012). Furthermore, expression QTL (eQTL) mapping, where gene expression levels are mapped across the genome similar to a behavioral phenotype, constructed a hierarchical gene network that is downstream of *Per3* (Wang et al., 2012). Future studies using computational and biological strategies have the potential to build models for system level interactions that may be involved in circadian disruption and drug taking.

Although it is often daunting to consider the numerous "ways" by which circadian rhythms regulate mood and reward neurocircuitry (Benedetti & Terman, 2013; McClung, 2013), the advent of new technologies accompanied by novel analytical approaches will help overcome past shortcomings. As technology continues to improve and becomes more accessible, researchers are more likely to adopt a systems approach that combines multiple technologies across species, such as neuroimaging and optogenetics, genetics, epigenetics, human postmortem, self-report, and sleep and activity monitoring (Edgar & McClung, 2013; Forbes & Dahl, 2012; Hasler & Clark, 2013; Hasler, Germain, et al., 2012; Li et al., 2013; Shumay, Logan, Volkow, & Fowler, 2012). Integrative translational systems approaches will be necessary to understand the role of the circadian system in substance use and abuse disorders and will be absolutely critical for determining whether treatments that target the circadian system are effective for treating addiction.

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