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A role for the circadian genes in drug addiction

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Summary

Diurnal and circadian rhythms are prominent in nearly all bodily functions. Chronic disruptions in normal sleep wake and social schedules can lead to serious health problems such as those seen in shift worker's syndrome. Moreover, genetic disruptions in normal circadian gene functions have recently been linked to a variety of psychiatric conditions including depression, bipolar disorder, seasonal affective disorder and alcoholism. Recent studies are beginning to determine how these circadian genes and rhythms are involved in the development of drug addiction. Several of these studies suggest an important role for these genes in limbic regions of the brain, outside of the central circadian pacemaker in the suprachiasmatic nucleus (SCN). This review summarizes some of the basic research into the importance of circadian genes in drug addiction.

Introduction

Drug addiction is a devastating disease that affects millions of people worldwide and contributes to the death of over 500,000 Americans per year (NIDA, 2007). The clinical picture of addiction is marked by compulsive drug use that the individual cannot fully control despite adverse consequences. Recent studies have revealed that this is likely a pathology of brain neuroplasticity (Kalivas and O'Brien, 2008). Repeated exposure to drugs of abuse leads to long-lasting changes that are not easily reversed in neuronal circuitry in specific brain regions. Some of these regions include the Nucleus Accumbens (NAc) and the Ventral Tegmental Area (VTA), both of which are part of the mesolimbic dopaminergic system and play a role in reward-related processes (Hyman et al., 2006). Although many aspects of drug addiction have been studied, there is still no truly effective treatment for this chronic disease. A high probability of relapse makes treatment and recovery very challenging. Understanding the molecular mechanisms that underlie the pathophysiological abnormalities that lead from drug use to addiction may help in designing new and more effective treatments. Interestingly, recent studies have suggested that the circadian clock, which controls the sleep/wake cycle and other physiological rhythms that cycle over twenty-four hours, plays an important role in drug addiction.

The Molecular Clock

Most living organisms exhibit daily cycles in behavior and physiology that enable them to adapt to their environment and react to a variety of stimuli known as Zeitgebers or "time-givers" (e.g. light, food, etc.). In mammals, the central pacemaker that controls most of these

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activity rhythms is located in the SCN of the anterior hypothalamus and is primarily entrained by light (Reppert and Weaver, 2001). In turn, the master clock in the SCN coordinates the timing and activity of other oscillators in other areas of the brain and in peripheral organs, like the kidney and liver (Reppert and Weaver, 2002). Thus, circadian clocks are present throughout the body and regulate a plethora of metabolic and behavioral rhythms. The molecular mechanisms that underlie the circadian clock have been conserved throughout evolution, from cyanobacteria and fungi to insects and mammals.

The circadian clock (Fig. 1) is based on a series of interconnected transcriptional positive-negative feedback loops that are regulated over the course of twenty-four hours in the absence of environmental input (Reppert and Weaver, 2001;Ko and Takahashi, 2006). In mammals, the circadian locomotor cycles kaput (CLOCK) and brain and muscle Arnt-like protein-1 (BMAL-1) proteins act as major transcriptional activators by forming a heterodimer that promotes transcription of the *Period* genes (*Per1*, *Per2*, and *Per3)*, the *Cryptochrome* genes *(Cry1* and *Cry2),* as well as many other genes by binding to E-box elements (CANNTG) in their promoters (Reppert and Weaver, 2001). Following translation of the PER and CRY proteins, they are phosphorylated by casein kinase 1 (CK1) ε and δ, and glycogen synthase kinase 3β (GSK3β). These phosphorylation events can alter PER and CRY stability, dimerization, and nuclear entry (Harms et al., 2003). The PER and CRY proteins dimerize and enter the nucleus to inhibit CLOCK-BMAL1 mediated transcription, hence creating a negative feedback loop. An adjoining oscillatory feedback loop that regulates the expression of *Bmal1* by binding to RORE elements in its promoter is composed of the nuclear receptor REV-ERBα and the transcriptional regulator RORA (Reppert and Weaver, 2001). In forebrain regions or in conditions where CLOCK is nonfunctional, Neuronal PAS domain protein 2 (NPAS2), a protein similar in structure and function to CLOCK, can induce expression of the *Per* and *Cry* genes (Reick et al., 2001;Debruyne et al., 2006). Interestingly, NPAS2, which has high expression in striatal regions, has been linked to the formation of emotional memory, sleep, and food entrainment (Garcia et al., 2000;Dudley et al., 2003;Franken et al., 2006). A major target of the master circadian clock is the pineal gland, which results in periodic discharge of the hormone melatonin. This hormone is exclusively released at night, even in nocturnal animals, and has been found to promote and regulate sleep and other rhythmic physiological events including seasonal adaptations (Pandi-Perumal et al., 2006).

Diurnal and Circadian Rhythms in Drug Addiction

Drug addiction has long been linked to disruptions in diurnal rhythms. For example, drug addicts generally have severe disruptions in their sleep/wake cycle, activity cycles, eating habits, as well as, abnormal rhythms in body temperature, hormone levels, and blood pressure (Wasielewsky et al., 2001; Jones et al., 2003). The disruptions in sleep following drug use are highly problematic, persist long after drug use has ceased, and very often lead to relapse (Jones et al., 2003). Many of these disruptions were originally thought to arise as an indirect result of chronic exposure to drugs of abuse, however, studies have shown that repeated drug use can directly affect ongoing diurnal rhythms. For example, cocaine exposure was found to alter the rhythms of autonomic, immune and sleep mechanisms (Irwin et al., 2007; Morgan et al., 2006). There is also a diurnal variation in the sensitivity to almost all drugs of abuse. Indeed, retrospective studies analyzing the admission of drug overdose patients in the emergency room of urban hospitals revealed that the majority of patients presented at around 6:30 pm compared to other times of day, suggesting a diurnal effect (Raymond et al., 1992), though there may be environmental and societal factors that influence this time of day effect as well. Additionally, addiction may be more prevalent in individuals with a compromised circadian clock, or with mood disorders which may have a circadian basis, such as Major Depressive Disorder, Bipolar Disorder, and Seasonal Affective Disorder, among others (Kandel et al., 2001; Grandin et al., 2006; McClung, 2007). The use of addictive drugs has been found to follow seasonal patterns,

with an increase in alcohol use predominantly during the winter, when individuals are more susceptible to depression (McGrath and Yahia, 1993). In addition, people with genetic sleep disorders and insomnia are more prone to addiction (Shibley et al., 2008).

Drug sensitivity is associated with rhythm abnormalities in animal models as well. Rats that were selectively bred based on a high preference for ethanol versus a low preference for ethanol have a shorter free-running period when animals are housed in constant light. One of the lines (the HAD line) also display a "splitting" of circadian activity in that they show two distinct bouts of activity in constant light which is not seen in the low ethanol preferring lines (Rosenwasser et al., 2005). A modest shortening of the free-running period was also found in ethanol-preferring mice compared to those selectively bred for low ethanol preference (Hofstetter et al., 2003). These results suggest that genetic ethanol preference is associated with abnormal circadian rhythms.

Drugs of Abuse Entrain Molecular and Behavioral Rhythms

Even though the master pacemaker is located in the SCN, circadian genes and proteins are widely expressed throughout the brain, thereby forming SCN-independent pacemakers that entrain to other non-photic stimuli such as food (Iijima et al., 2002; Stephan, 1984). Drugs of abuse can also serve as powerful Zeitgebers for some of these clocks outside of the SCN. Several studies have shown that drugs of abuse, like cocaine, methamphetamine, nicotine and alcohol, can entrain locomotor activity rhythms (Kosobud et al., 2007). Furthermore, in rodents with a lesioned SCN, methamphetamine in the drinking water restores their activity rhythms in a robust manner, and animals can be entrained to daily methamphetamine injections (Iijima et al., 2002; Masubuchi et al., 2000). Interestingly, methamphetamine treatment shifts the expression of the *Per* genes in striatal regions in a manner that matches the shifts in activity rhythms and is independent from the SCN rhythms (Iijima et al., 2002). Furthermore, acute methamphetamine treatment leads to a rapid induction of *mPer1*, but not *mPer2* or *mPer3* expression in the dorsal striatum (Nikaido et al., 2001). This suggests that the induction of circadian genes in these regions is specific, or that *mPer1* responds to cocaine as an immediate early gene. Indeed, rapid induction of *mPer1* is seen in the SCN in response to light (Crosio et al., 2000). Circulating melatonin rhythms remained unaffected by these treatments however; melatonin receptors are differentially regulated in the striatum following chronic cocaine treatment (Imbesi et al., 2006). There are no known direct projections from the SCN to the striatal regions, so melatonin could be a factor which synchronizes these regions. Interestingly, pinealectomy abolishes *Per1* rhythms in striatal regions, but has no effect on rhythms in other limbic regions of the brain including the oval nucleus of the bed nucleus of the stria terminalis, the central nucleus of the amygdala, and the hippocampus (Amir et al., 2006). However, it is still unclear what the role for melatonin is in mediating drug-induced responses. It is possible that changes in melatonin signaling in striatal regions could lead to alterations in mood, motivation, or other processes related to addiction.

The Response to Drug Exposure is Different over the Light/Dark Cycle

Several animal studies of addiction have shown that there are diurnal differences in drug-induced behavioral responses, specifically locomotor activity, drug sensitivity, sensitization, conditioned place preference (CPP), and self-administration. A study by Baird and Gauvin found that rats display an increase in the sensitivity to the reinforcing properties of cocaine at 1:00am and 1:00pm compared to rats tested at 7:00am and 7:00pm, indicated by self-administration at lower doses and decreased drug intake (Baird and Gauvin, 2000). However, in general rats show a striking diurnal pattern of self-administration with a greater intake during the active dark phase than during the light phase (Lynch et al., 2008; Roberts et al., 2002). Interestingly, cocaine intake is significantly increased and the diurnal pattern of intake is nearly

abolished when animals are given high doses of cocaine (2.5 mg/kg) or access to more trials (Roberts et al., 2002). This loss of diurnal intake rhythms may be very important in the development of addiction in which there is a loss of control and escalation of drug intake that interferes with normal activity (Ahmed and Koob, 1998). In contrast to the self-administration studies, mice treated for several days with cocaine during the day show a greater level of sensitization than those treated at night (Akhirasoglu et al., 2004; Abarca et al., 2002). Moreover, conditioned place preference for cocaine also displays a diurnal rhythm, with greater effects seen when drug is given during the day than during the night (Kurtuncu et al., 2004; Abarca et al., 2002). Intriguingly, studies performed in rats revealed that in opposition to short-term sensitization, long-term sensitization (2 weeks after last injection) was greater when the drug was given at the onset of the dark phase (Sleipness et al., 2005). These studies suggest that there is a change in the reward value for the drug and locomotor sensitivity to the drug over the light/dark cycle that is still not well understood.

A recent study by Sleipness et al. (2007) found that the SCN plays a role in the diurnal regulation of cocaine reward-related behavior. In this study, the authors found that acquisition of CPP behavior was tonically influenced by the SCN, as extinction of CPP behavior was SCN-dependent and reinstatement of CPP behavior was SCN-independent, suggesting an extra-SCN oscillator at work in mediating this behavior (Sleipness et al., 2007a). Many of these diurnal differences in models of addiction may be due to diurnal regulation of dopaminergic transmission in the mesolimbic pathway. In fact, rhythms of cocaine sensitivity correlate with rhythms in postsynaptic levels of dopamine and the activity of the dopaminergic receptors in striatal regions (Naber et al., 1980). Interestingly, studies in *Drosophila* found that dopamine receptor responsiveness displays a diurnal modulation (Andretic and Hirsh, 2000). Additionally, in mammals the expression of nearly all of the elements involved in dopaminergic transmission have a diurnal rhythm, including the dopamine receptors, the dopamine transporter, and tyrosine hydroxylase (Weber et al., 2004; Schade et al., 1995; Shieh et al., 1997). These diurnal differences in dopamine transporter and tyrosine hydroxylase expression levels are somewhat SCN-dependent, since SCN-lesioned animals have dampened rhythms in comparison to sham controls (Sleipness et al., 2007b). Moreover, a recent study by Hampp et al. (2008) found that the monoamine oxidase A (MAOA) gene, which metabolizes dopamine, is a transcriptional target of BMAL1 and the PER2 protein. PER2 positively regulates its expression and mice with a mutation in *Per2* ($Per2^{Brdm1}$) have a decrease in *Maoa* expression in the NAc and VTA. These mice also have an increase in midbrain dopamine levels and release and an increase in the sensitization to cocaine (Hampp et al., 2008; Abarca et al., 2002).

In response to drugs of abuse, mesocorticolimbic dopaminergic activity leads to long lasting plasticity in the glutamatergic projections from the prefrontal cortex to the primarily GABAergic NAc (Kalivas, 2007). This altered plasticity is thought to be very important in the development of addiction (Kalivas, 2007). Extracellular levels of glutamate (Glu) and gamma-aminobutyric acid (GABA) in the dorsal striatum and NAc have both a diurnal pattern in light/dark conditions and a circadian rhythm in constant conditions with highest levels at night (Castaneda et al., 2004). Perfusion with melatonin prevents the daytime decrease in both Glu and GABA levels thereby dampening the rhythm (de Prado et al., 2000). This suggests that melatonin regulates striatal rhythms in Glu and GABA transmission. Moreover, expression of the vesicular glutamate transporter 1 (VGlut1) protein in synaptic vesicles has a diurnal rhythm with high levels at the start of the light period which decline by noon, rise again at the start of the dark period and fall again at midnight (Yelamanchili et al., 2006). Mice lacking *Per2* do not have any rhythm in *VGlut1* expression, suggesting that components of the circadian clock regulate glutamatergic vesicular sorting. Furthermore, mice with a mutation in *Per2* also show an increase in glutamate levels on the extracellular space of the NAc, due in part to a reduction in levels of the glutamate transporter *Eaat1*, and this increase in glutamate is involved in the increased alcohol intake measured in these mice (Spanagel et al., 2005). Thus *Per2* plays an

important role in regulating the expression of key genes involved in glutamatergic transmission in the striatum.

Circadian Genes in Animal Models of Addiction

Animal studies of drug responsiveness, sensitization, and reward have found that the circadian genes are important regulators of the behavioral responses to drugs of abuse. The first studies that revealed this relationship were done in *Drosophila*, and found that flies with mutations in the circadian genes *Per, Clock, Cycle,* or *Doubletime* all fail to sensitize to cocaine following repeated exposure, while those that had a mutation in the *Timeless* gene showed normal cocaine responses (Andretic et al., 1999). These pioneering studies provided evidence for the impact of specific circadian genes on addictive processes, which might be conserved throughout evolution. Following these studies, several studies found that cocaine is able to induce or repress specific circadian gene expression in various regions of the mammalian brain. Yuferov *et al.* found that *rPer1* was induced in the dorsal striatum following acute cocaine, while *rPer2* was only induced following a chronic “binge” pattern of cocaine (Yuferov et al., 2003). Furthermore, Uz *et al.*, found that chronic cocaine treatment (rather than acute in most cases) resulted in the up or downregulation of several circadian genes in both the striatum and hippocampus (Uz et al., 2005a). These changes were distinct from those observed after chronic treatment with the antidepressant, fluoxetine. Our group has also found that the *Period* genes as well as *Npas2* are regulated in striatal regions in response to chronic cocaine (Peevey et al., submitted; McClung and Nestler, 2003). Moreover, a recent microarray study in animals self-administering cocaine found that with one day of withdrawal, 29 genes were differentially regulated in the striatum that are known to have a circadian function or be associated with the circadian system (Lynch et al., 2008). Using pathway analysis software, Lynch et al. found that indeed changes to the circadian system represented the most significantly altered pathway following cocaine self-administration in the striatum (Lynch et al., 2008). These results suggest that alterations in the molecular clock in the striatum are important in a relevant model of addiction.

The importance of the circadian genes in cocaine preference was first shown by Abarca et al., who found that mice that lack a functional *mPer1* gene failed to sensitize to cocaine and show a complete lack of cocaine reward as measured by CPP. In contrast, mice that lack *mPer2* exhibited a hypersensitized response after repeated drug exposure with no change in cocaine-induced place preference (Abarca et al., 2002). In addition, *mPer1* may partially regulate morphine dependence, since mice treated with a DNAzyme towards this gene and morphine simultaneously show a reduction in the conditioned preference for the drug, while those that were treated with the DNAzyme after the morphine treatment did not show a difference when compared to the control group (Liu et al., 2005). This regulation of morphine reward by *mPer1* could be through its regulation of extracellular signal-regulated kinase (ERK) signaling since targeted disruption of *mPer1* by DNAzyme prevents the increase in ERK expression that is seen following morphine treatment (Liu et al., 2007). Further studies have found that *mPer2* is involved in influencing alcohol consumption. Spanagel and colleagues found that mice carrying a mutation in the PAS domain of *Per2* have an increase in alcohol intake that is linked to changes in glutamatergic transmission (Spanagel et al., 2005). The authors also found that variations in the *Per2* gene in humans are linked to modulation of alcohol intake, making these variations functionally relevant to human addiction.

Studies from our lab have also identified a role for the *Clock* gene in cocaine reward and dopaminergic transmission. Mice with a mutation in the *Clock* gene (Δ19) show a robust sensitization to cocaine, an increase in cocaine preference, and an increase in the reward value for cocaine as measured by intracranial self-stimulation following cocaine treatment (McClung et al., 2005; Roybal et al., 2007). These mice also have an increase in dopaminergic activity

in the VTA which may be responsible for the increase in reward value for cocaine (McClung et al., 2005). This includes an increase in dopamine cell firing, bursting, and levels of TH and phosphor-TH (McClung et al., 2005). In further studies it was found that these mice display a complete behavioral profile that is very similar to human bipolar patients in the manic state (Roybal et al., 2007). This is interesting since mania is very often associated with an increase in psychostimulant use (Brown, 2005). Intriguingly, in a separate group of studies, we found that in contrast to the *Clock* mutant mice, *Npas2* mutant mice show a decrease in cocaine preference (Peevey et al., submitted). Additionally, *Npas2* expression and activity is enhanced in striatal regions following chronic cocaine treatment while *Clock* levels remain unchanged. (Peevey et al., submitted). Thus, NPAS2 and CLOCK might have distinct functions in limbic regions in the modulation of cocaine reward.

Conclusions

More and more studies are identifying an important role for circadian rhythms and the genes that make up the circadian clock in the development of drug addiction. Drug addicts generally have very disrupted diurnal rhythms and this suggests that abnormal clock function may lead to an increased vulnerability for addiction. This may be particularly true for people whose drug abuse coincides with periods of depression or mania. Furthermore, drugs of abuse are able to entrain both molecular and behavioral rhythms by altering clocks in limbic brain regions that are able to function in a manner independent of the SCN. Moreover, drugs of abuse alter the expression of circadian genes in reward-related regions of the brain, and the removal of specific circadian genes affects the sensitivity and reward value for several different drugs of abuse. Since the removal of specific genes leads to different responses, it is possible that these circadian genes are serving independent functions in regulating drug responses that are unrelated to their roles in circadian rhythms. It is also possible that these differences are due to the different functions of specific genes in the negative feedback loop that controls rhythms. Moreover, if drugs of abuse are entraining reward-related clocks in brain regions outside of the SCN, this might lead to an increase in drug seeking and craving at the time of day when drugs are anticipated. Future studies will help elucidate the important functions of these genes in the development of addiction.

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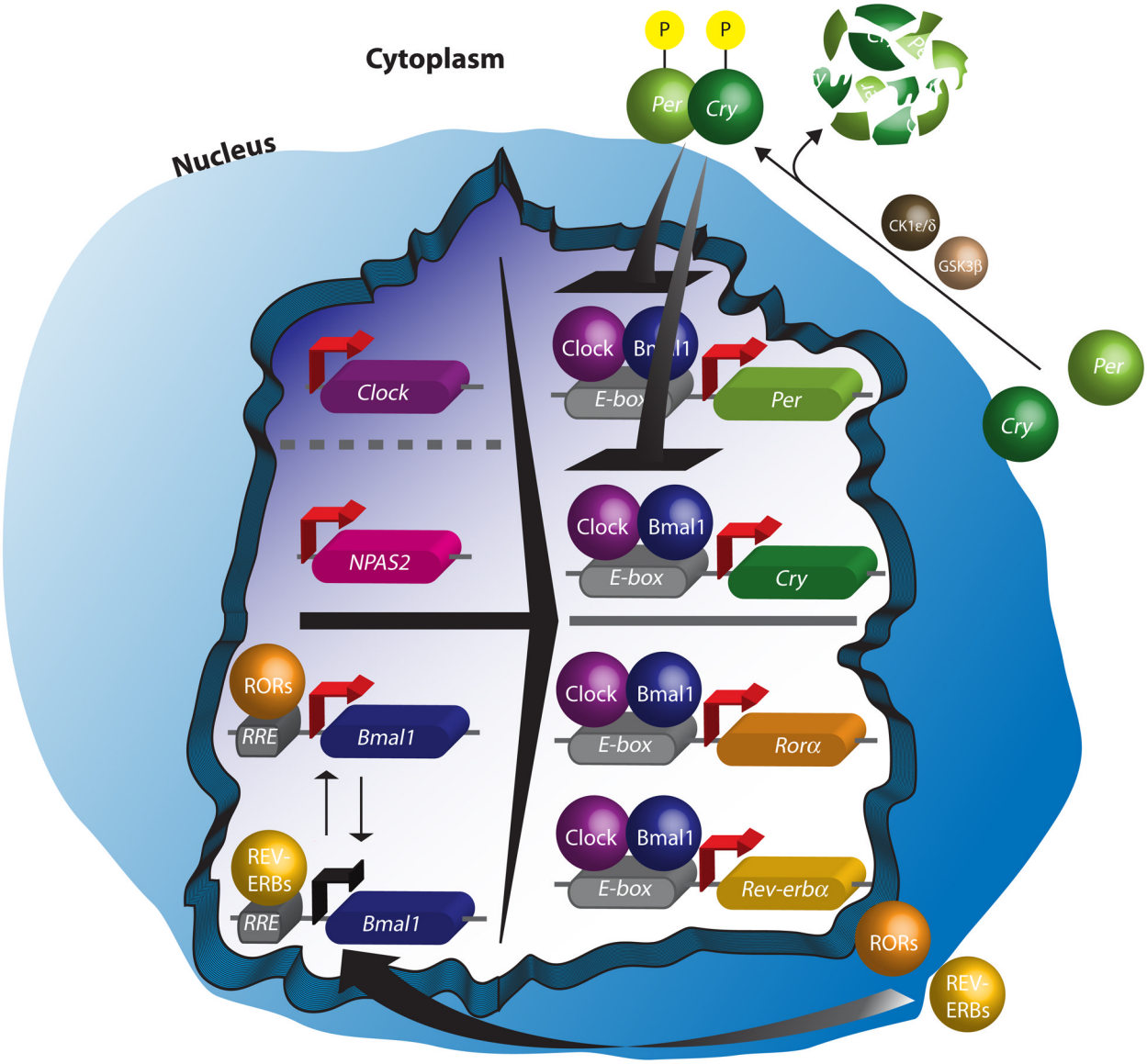

Figure 1.
Cartoon depicting the molecular clock. CLOCK and BMAL1 (or NPAS2 and BMAL1) regulate the expression of the *Period* and *Cryptochrome* genes. These are translated in the cytoplasm and are phosphorylated. They enter the nucleus and inhibit the activity of CLOCK:BMAL1. A separate loop depicted at the bottom of the nucleus shows the regulation of *Bmal1* by Rorα and Rev-erbα.