Physiology & Behavior 143 (2015) 58–69

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Review

# Diurnal and circadian regulation of reward-related neurophysiology and behavior

Ian C. Webb [a,*], Michael N. Lehman [a], Lique M. Coolen [a,b]

[a] Dept. of Neurobiology and Anatomical Sciences, University of Mississippi Medical Center, Jackson, MS, USA
[b] Dept. of Physiology & Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

## HIGHLIGHTS

- Drug reward varies across the 24 hour day.
- Rhythms in drug reward are associated with rhythmic mesocorticolimbic activity.
- Circadian clock genes regulate reward-related behavior and neurophysiology.
- Drug administration influences mesocorticolimbic circadian clock gene expression.

## ARTICLE INFO

*Article history:*
Received 10 December 2014
Received in revised form 9 February 2015
Accepted 17 February 2015
Available online 21 February 2015

*Keywords:*
Addiction
Mesolimbic
Rhythm
Clock gene

## ABSTRACT

Here, we review work over the past two decades that has indicated drug reward is modulated by the circadian system that generates daily (i.e., 24 h) rhythms in physiology and behavior. Specifically, drug-self administration, psychomotor stimulant-induced conditioned place preference, and locomotor sensitization vary widely across the day in various species. These drug-related behavioral rhythms are associated with rhythmic neural activity and dopaminergic signaling in the mesocorticolimbic pathways, with a tendency toward increased activity during the species typical wake period. While the mechanisms responsible for such cellular rhythmicity remain to be fully identified, circadian clock genes are expressed in these brain areas and can function locally to modulate both dopaminergic neurotransmission and drug-associated behavior. In addition, neural and endocrine inputs to these brain areas contribute to cellular and reward-related behavioral rhythms, with the medial prefrontal cortex playing a pivotal role. Acute or chronic administration of drugs of abuse can also alter clock gene expression in reward-related brain regions. Emerging evidence suggests that drug craving in humans is under a diurnal regulation and that drug reward may be influenced by clock gene polymorphisms. These latter findings, in particular, indicate that the development of therapeutic strategies to modulate the circadian influence on drug reward may prove beneficial in the treatment of substance abuse disorders.



**Contents**



* Corresponding author at: Dept. of Neurobiology and Anatomical Sciences, University of Mississippi Medical Center, 2500 North State St., Jackson, MS 39216-4505, USA.
*E-mail address:* iwebb@umc.edu (I.C. Webb).

http://dx.doi.org/10.1016/j.physbeh.2015.02.034
0031-9384/

## 1. Introduction

Addiction is defined as the compulsive seeking and taking of drugs regardless of the known negative consequences. Drugs of abuse act as rewards (i.e., stimuli with intrinsic positive value) and reinforce the behaviors necessary to obtain them. Repeated drug administration can induce neuroplastic changes in the mesocorticolimbic brain regions associated with reward seeking, impulsivity, and emotional regulation, ultimately resulting in the addictive phenotype [1,2]. Despite recent advances in our understanding of the neurobiology of addiction, individuals undergoing treatment for substance abuse disorders exhibit a high rate of relapse, even after prolonged periods of drug abstinence [3]. Hence, more effective therapies are needed, the development of which hinges on advances in our understanding of the cellular and molecular mechanisms involved in the development and maintenance of addictive behavior.

The circadian system, which produces daily (i.e., ~24 h) rhythms in physiology and behavior [4,5] consists of a hierarchy of tissue- and cell-level oscillators located in both the periphery and brain [6], including brain regions associated with reward processing [7,8]. Work over the past couple of decades has established a circadian influence on reward-related behavior and neurophysiology [9–11]. Thus, understanding how the circadian system normally modulates reward processing and how this influence changes with repeated drug administration may provide novel insights into the pathophysiology of addiction and suggest new avenues for treatment. Here, we review the literature on daily rhythms in drug reward and mesocorticolimbic neurophysiology, discuss the potential underlying mechanisms, and summarize the bidirectional interactions between drug intake and circadian clock gene expression.

## 2. Circadian rhythms

Circadian rhythms in behavior and physiology, which persist in the absence of environmental timing cues, allow the organism to anticipate and to adapt to the regular daily events that result from the earth's rotation on its axis. These daily rhythms are coordinated by the hypothalamic suprachiasmatic nucleus (SCN), which receives retinal input and synchronizes the internal milieu to the external world [12–15]. Within the SCN, circadian rhythms in cellular activity are generated by self-sustaining, inter-locking transcriptional/translational loops where the protein products of so-called circadian clock genes feedback to inhibit their own transcription with a period of about 24 h [16–18]. Classically, the SCN was conceptualized as a singular master circadian pacemaker that induced rhythmicity in other structures. We now know that many tissues, particularly peripheral tissues, show rhythmic clock gene expression in the absence of SCN input [4,6,19]. However, most brain regions (with the exception of the retina and olfactory bulb; [20–22]) when isolated from the SCN cease circadian rhythms in cellular activity, either immediately or after several cycles [23]. Thus, some brain regions can be classified as slave oscillators that require SCN input to cycle while others act as semi-autonomous oscillators that need continued SCN input to generate a coherent rhythm [24].

According to the prevailing molecular model of the circadian clock, transcription is initiated by the circadian clock gene protein products CLOCK and BMAL1, which dimerize and bind to E-boxes to induce the expression of *period* (*per 1*, *2* and *3*) and *cryptochrome* (*cry 1* and *2*) genes [25,26]. PER and CRY dimerize, translocate to the nucleus, and inhibit the transcriptional action of the CLOCK:BMAL1 heterodimer [27–29]. NPAS2 is a functional homolog of CLOCK expressed primarily in the forebrain that can also bind BMAL1 to induce the expression of *per* and *cry* genes [30,31]. As PER and CRY levels decrease, inhibition of CLOCK:BMAL1 subsides, thus reinitiating the cycle. Secondary loops involving REV-ERBα and ROR regulate *bmal1* transcription, and post-translational modifications control the stability and cellular localization of clock proteins, thus contributing to the ~24 h period of the molecular oscillation [32–35].

Circadian clock genes act as transcriptional regulators of so-called clock-controlled genes and can regulate cellular processes via this influence. At the whole animal level, these cellular processes are ultimately manifested as circadian rhythms in general physiology and behavior.

## 3. Diurnal rhythms in reward-related behavior

Diurnal rhythms in drug self-administration have been reported across various animal models with peak intake usually observed during

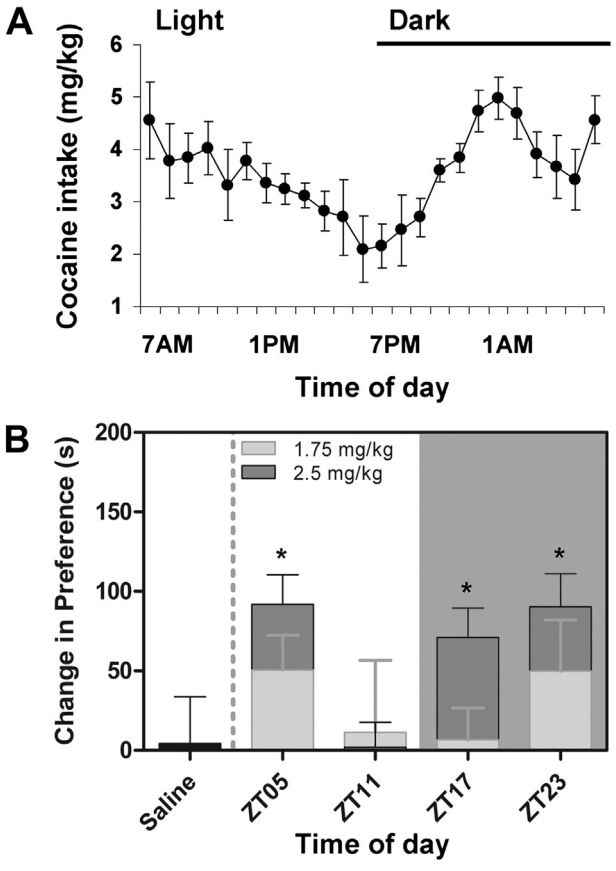


**Fig. 1.** Diurnal rhythms in drug self-administration and conditioned place preference. A) Cocaine self-administration in a rat over the course of a day. Mean (±SE) hourly cocaine intake across the light/dark cycle averaged across 4 days under a discrete trials procedure. Reprinted from Brain Research, 1213, Lynch WJ, Girgenti MJ, Breslin, FJ, Newton SS, Taylor JR, Gene profiling the response to repeated cocaine self-administration in the dorsal striatum: a focus on circadian genes, 166–77, 2008, with permission from Elsevier. B) Diurnal rhythm in the conditioned place preference induced by two systemic doses of amphetamine. Data are expressed as mean ± SEM. * = significantly different from ZT11 and a saline control at the 2.5 mg/kg dose. Reprinted from the Journal of Biological Rhythms, 24, Webb IC, Baltazar RM, Wang X, Pitchers KK, Coolen LM, Lehman, MN, Diurnal variations in natural and drug reward, mesolimbic tyrosine hydroxylase, and clock gene expression in the male rat, 465–76, 2009, with permission from SAGE.