Alcohol 49 (2015) 341–349

Contents lists available at ScienceDirect

Alcohol

journal homepage: http://www.alcoholjournal.org/

Circadian clock genes: Effects on dopamine, reward and addiction

Puja K. Parekh [a,1], Angela R. Ozburn [a,b,c,1], Colleen A. McClung [a,*]

[a] University of Pittsburgh School of Medicine, Department of Psychiatry, 450 Technology Drive, Suite 223, Pittsburgh, PA 15219, USA
[b] Portland Veterans Affairs Medical Center, Research and Development Service, Portland, OR 97239, USA
[c] Oregon Health and Science University, Department of Behavioral Neuroscience, Portland, OR 97239, USA

ARTICLE INFO

Article history:
Received 8 August 2014
Received in revised form
2 September 2014
Accepted 3 September 2014

Keywords:
Circadian
Dopamine
Alcohol
Addiction

ABSTRACT

Addiction is a widespread public health issue with social and economic ramifications. Substance abuse disorders are often accompanied by disruptions in circadian rhythms including sleep/wake cycles, which can exacerbate symptoms of addiction and dependence. Additionally, genetic disturbance of circadian molecular mechanisms can predispose some individuals to substance abuse disorders. In this review, we will discuss how circadian genes can regulate midbrain dopaminergic activity and subsequently, drug intake and reward. We will also suggest future directions for research on circadian genes and drugs of abuse.

Introduction

The majority of living organisms display 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.). Circadian rhythms enable organisms to adaptively entrain to their environmental conditions to optimize behavioral responses for survival. The central rhythm-generating nucleus in the mammalian brain is the suprachiasmatic nucleus (SCN) of the hypothalamus. Additional subsidiary oscillators have been identified in extra-SCN brain regions and peripheral tissues and these can be coordinated by the SCN or independently controlled (Reppert & Weaver, 2002). Circadian molecular clock machinery is present in all cell types throughout the body. This mechanism consists of an interconnected series of core and accessory transcriptional-translational feedback loops modulated by regulatory kinases (see Fig. 1). The activity of the clock components is regulated over a diurnal timescale. Integral to the mammalian circadian clock are the transcription factors, Circadian Locomotor Output Cycles Kaput (CLOCK), or Neuronal PAS Domain Protein 2 (NPAS2) and Brain and Muscle Arnt-like Protein 1 (BMAL1). These proteins heterodimerize and promote transcription of the *Period* (*Per1, Per2, Per3*) and *Cryptochrome* (*Cry1, Cry2*) genes. Throughout the 24-hour day, PER and CRY proteins in turn are phosphorylated and feed back into the nucleus to inhibit the transcriptional activity of the CLOCK/NPAS2-BMAL1 complex, and hence their own expression. CLOCK/NPAS2 and BMAL1 additionally regulate the transcription of many other genes by binding to E-box elements in their promoter regions. Among these clock-controlled genes are those that underlie aspects of neuronal signaling in mesolimbic systems involved in reward processing and the development of addictive behaviors (Abarca et al., 2002; Gamsby et al., 2013; Logan, McCulley, Seggio, & Rosenwasser, 2012; McClung et al., 2005; Vitaterna et al., 2006).

In addition to the SCN, midbrain and forebrain regions express molecular clock elements at the cellular level and are also indirectly connected with the SCN through anatomical projections (see Fig. 2). Mesocorticolimbic brain circuitry has been shown to be important for the processing of rewarding stimuli, including drugs of abuse, which can remodel the system to cause addiction in vulnerable individuals. Major components of this circuitry that are important for alcohol responses include the ventral tegmental area (VTA), nucleus accumbens (NAc), amygdala, hippocampus, and medial prefrontal cortical regions. Koob and Volkow (2010) review decades of clinical and pre-clinical studies showing that discrete aspects of mesocorticolimbic circuitry are engaged during binge drug use, withdrawal/negative effect, and relapse, encompassing all stages of the addiction cycle (Koob & Volkow, 2010). Much progress has been made in the identification of molecular and physiological adaptations that underlie substance use disorders. The neurotransmitter dopamine (DA) features prominently in the behavioral response to drugs of abuse as well as natural rewards. Activation of the

* Corresponding author. Tel.: +1 412 624 5547.
E-mail address: mcclungca@upmc.edu (C.A. McClung).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.alcohol.2014.09.034
0741-8329/

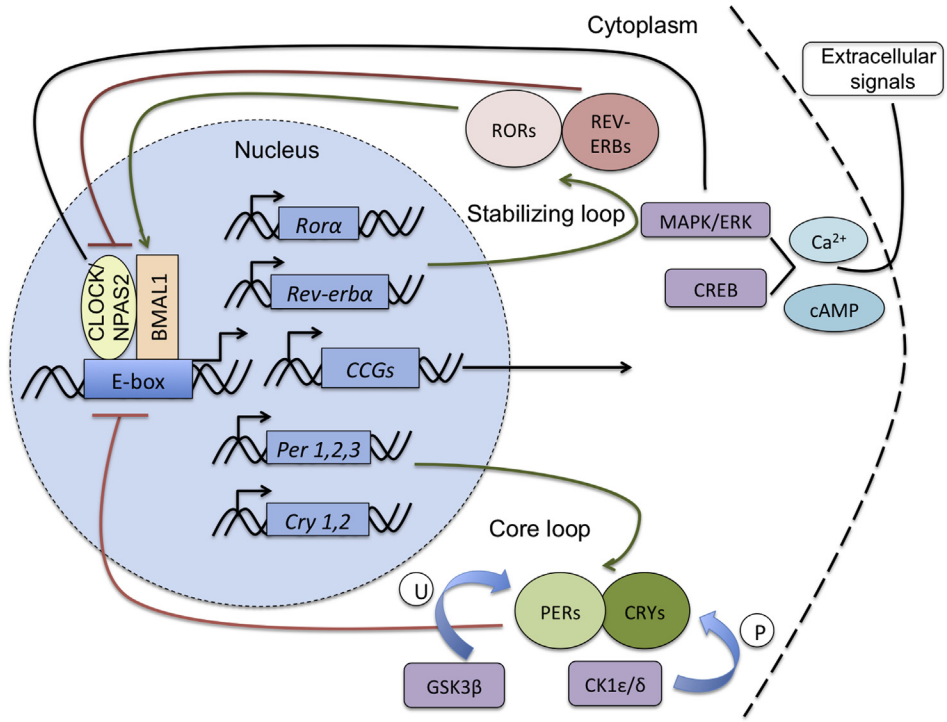

Fig. 1. A series of transcriptional and translational feedback loops comprise the core molecular clock in mammals. At the heart of the clock are the transcription factors CLOCK (or NPAS2) and BMAL1 which heterodimerize in the nucleus and bind to Enhancer Box (E-box) sequences in many genes to regulate their transcription. Targets include the *Per* and *Cry* genes. Over the course of 24 h, PER and CRY proteins dimerize and shuttle back into the nucleus where CRY directly inhibits the CLOCK/NPAS2-BMAL1 complex forming a negative feedback mechanism. Additionally, CLOCK/NPAS2 and BMAL1 also regulate the expression of the nuclear hormone receptors Rev-erbα and Rorα, which can repress or activate *Bmal1* transcription. Other regulatory proteins act on the molecular clock through phosphorylation including Casein kinase 1 (CK1) proteins and ubiquitination by Glycogen synthase kinase beta (GSK3β). Intracellular calcium signaling cascades can also act to regulate the activity of core circadian proteins through kinase-dependent pathways. CCGs, Clock controlled genes; P, phosphorylation; U, ubiquitination.

midbrain DA system can confer incentive salience to environmental stimuli and promote motivational or goal-directed behavior (Berridge & Robinson, 1998; Nestler, 2005). The time course of this signaling has been shown to correspond to reward value and predicted outcomes (Robinson & Berridge, 1993; Schultz, 2006; Schultz, Dayan, & Montague, 1997). This role of dopamine goes beyond serving a hedonic purpose to one that motivates behavior in the direction of obtaining a pleasurable substance, as dopamine depletion does not abolish unconditioned affective reaction patterns to sucrose and quinine (Berridge & Robinson, 1998). These principles also support a reinforcement learning model of dopamine action, which contributes to goal-oriented behavior (Montague, Hyman, & Cohen, 2004). Reinforcement learning models help explain the unique advantage of addictive drugs over natural reinforcers in that rapid pharmacokinetic and prolonged effects of drugs on dopamine release may promote overlearning on drug-related stimuli including cues (Hyman, 2005; Montague et al., 2004). Elements of the dopaminergic system and reward have been shown to be under circadian regulation. Diurnal variations observed in the rewarding value of natural and drug reinforcers suggest that within distinct regions of the mesocorticolimbic system, rhythms in expression of circadian and dopamine-related proteins may coincide with rhythms in reward behavior to promote dependence (Baltazar, Coolen, & Webb, 2013; Webb et al., 2009). A conceptual model of the interaction between circadian misalignment, mesocorticolimbic circuitry and the development of alcohol use disorders (AUDs) in adolescents has been proposed by Hasler and Clark (2013). In this review we will highlight a number of recent studies providing strong evidence that circadian genes regulate several aspects of dopaminergic transmission.

Although the master pacemaker is located in the SCN, circadian genes and proteins are widely expressed throughout the brain and periphery, thereby forming SCN-independent pacemakers that entrain to other non-photic stimuli including food and drugs (Iijima, Nikaido, Akiyama, Moriya, & Shibata, 2002; Stephan, 1984). Many studies have established that addictive drugs are able to serve as zeitgebers and can reliably entrain anticipatory activity rhythms in animals when given regularly. This locomotor activity has been likened to the seeking behavior characteristic of drug addiction. Additionally, the circadian regulation of dopamine transmission and signaling plays a role in reward (Kosobud et al., 2007). For example, daily methamphetamine injections have been shown to entrain animals and induce anticipatory locomotor activity to the time of injection (Kosobud, Pecoraro, Rebec, & Timberlake, 1998). Ethanol, cocaine, and nicotine have also been shown to induce this anticipatory behavior and alter behavioral rhythms (Gillman, Kosobud, & Timberlake, 2008; Kosobud et al., 2007; White, Feldon, Heidbreder, & White, 2000). In rodents with SCN lesions methamphetamine in the drinking water restores activity rhythms in a robust manner (Masubuchi et al., 2000). In addition, methamphetamine treatment shifts the expression of the *Per* genes in striatal regions in a manner that matches shifts in activity rhythms, independent of the SCN rhythms (Iijima et al., 2002). Rewarding stimuli such as food or chocolate can entrain both behavioral and *Per1* expression rhythms, which persist for several days in several brain regions (including dorsal medial hypothalamus, nucleus accumbens, prefrontal cortex, and the central amygdala) (Ángeles-Castellanos, Salgado-Delgado, Rodríguez, Buijs, & Escobar, 2008). Therefore, both behavioral and molecular rhythms appear to be affected by rewarding stimuli, including drugs of abuse.