Published in final edited form as:

Pharmacol Biochem Behav. 2013 August ; 109: 8–15. doi:10.1016/j.pbb.2013.04.010.

A Novel Model of Chronic Sleep Restriction Reveals an Increase in the Perceived Incentive Reward Value of Cocaine in High Drug-Taking Rats

Matthew D. Puhl¹, Matthew Boisvert¹, Zhiwei Guan², Jidong Fang^{2,*}, and Patricia S. Grigson^{1,*}

¹Department of Neural and Behavioral Sciences, The Pennsylvania State University College of Medicine, Hershey, PA 17033

²Department of Psychiatry, The Pennsylvania State University College of Medicine, Hershey, PA 17033

Abstract

Substance abuse and sleep deprivation are major problems in our society. Clinical studies suggest that measures of poor sleep quality effectively predict relapse to substance abuse. Previously, our laboratory has shown that acute sleep deprivation increases the rate and efficiency (i.e., the goal-directed nature of responding) of cocaine self-administration using a progressive ratio (PR) schedule of reinforcement. However, the problem of sleep deprivation in our nation is largely one of chronicity. Therefore, the current study used a rodent model of chronic sleep restriction more akin to that experienced by humans (approximately 40% reduction in baseline sleep over the course of 8 days) to assess the impact of chronic sleep deprivation on cocaine-seeking and cocaine-taking behaviors in rats early during acquisition of self-administration. While low drug-taking rats were unaffected by chronic sleep restriction, high drug-takers in the chronic sleep restriction (CSR) group exhibited enhanced fixed ratio (FR) responding by the fourth day of FR training and significantly higher PR breakpoints than their non-sleep restriction (NSR) counterparts. This study is the first to directly assess the impact of chronic sleep deprivation on drug self-administration. These results show that chronic sleep deprivation early during acquisition of self-administration has a significant effect on the perceived incentive reward value of cocaine in high drug-takers, as indicated by both increased FR responding and an increased willingness to work for drug. Thus, it is important to be mindful of such factors in clinical settings designed for treatment of addiction and relapse prevention.

Keywords

chronic sleep restriction; cocaine; disc treadmill method; fixed ratio; progressive ratio; self-administration

© 2013 Elsevier Inc. All rights reserved.

Address correspondence to: Patricia S. Grigson, The Pennsylvania State University College of Medicine, Department of Neural and Behavioral Sciences, 500 University Drive, H181, Hershey, PA 17033, Phone: (717) 531-5772, Fax: (717) 531-6916, psg6@psu.edu.
*indicates equal contribution to this work

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

Substance abuse and drug addiction persist as major problems in the United States. In fact, the lifetime prevalence of substance dependence is 18% among Americans (Gillin and Drummond, 2000). In addition, substance abuse incurs an estimated \$484 billion in annual expenses to our nation (National Institute on Drug Abuse, 2005). The severity of the problem and difficulty of treatment are further compounded by the fact that addiction is a chronic, relapsing disease that induces long-lasting changes in brain function that interact with numerous environmental factors (O'Brien, 2001). Those interactions, then, greatly increase susceptibility to relapse. In fact, it has been reported that up to 90% of human addicts will relapse to drug seeking, even after a prolonged period of abstinence (DeJong, 1994). Clinical studies suggest that sleep deprivation is one such factor, and both subjective (self-administered questionnaire scores) and objective (polysomnographic sleep parameters) measures of poor sleep quality have been shown to predict relapse in humans (Brower, 2001; Clark et al., 1998; Foster and Peters, 1999; Gillin et al., 1994). Also, acute sleep deprivation has been shown to increase preference for methylphenidate (Roehrs et al., 1999, 2004). In addition, we have previously demonstrated in rats that acute sleep deprivation increases the rate and efficiency (i.e., the goal-directed nature of responding) of cocaine self-administration during PR testing, even in rats that maintain low levels of drug intake (i.e., low drug-takers; Puhl et al., 2009).

The majority of the scientific literature on sleep deprivation (including the studies cited above) focuses on acute sleep deprivation (i.e., a discrete block of sleep deprivation usually 1-24 h in duration). While these studies have been extremely important in identifying the cognitive, physical, and behavioral effects of sleep deprivation, the problem of sleep deprivation in the United States is largely one of chronicity (National Sleep Foundation, 2008). Thus, even though acute sleep loss (e.g., "pulling an all-nighter" to finish a work- or school-related project, staying out late on the weekends, etc.) is troublesome, the majority of Americans report maintaining 6 h of sleep or less per night (a 25% reduction of the recommended 8 h) over the course of months, or even years (Hale and Do, 2007; Jean-Louis et al., 2000). Therefore, a model of chronic sleep restriction is more appropriate for the investigation of the impact of sleep deprivation on substance abuse and addiction. Unfortunately, a limited number of studies have employed the chronic sleep restriction method and none have assessed the impact of chronic sleep deprivation on responding for abused substances. Here we are interested in responding for cocaine early during the acquisition phase of self-administration, given that it is during this period of initial exposure that changes in neuroplasticity are particularly robust, resulting in long-lasting changes in the response to drug (Ciccocioppo et al., 2004). Therefore, the present study evaluated the effects of chronic sleep restriction, akin to that experienced by humans, on the acquisition of cocaine-seeking and cocaine-taking behaviors in a rodent model.

2. Methods

2.1. Subjects

This study was conducted in three replications. The subjects were 24 (n=8 for Replications 1-3) naïve, male Sprague-Dawley rats (Charles River Laboratories, Raleigh, NC), approximately three months of age at the beginning of the experiment. Due to disruption of EEG/EMG electrode placement, one rat was eliminated from the study. In addition, two rats displayed extremely erratic sleep patterns and also were eliminated from the study. Except where otherwise noted, rats were housed individually in standard wire mesh cages, in a colony room with temperature, humidity, and ventilation controlled automatically. Rats were maintained on a 12/12 h light/dark cycle, with lights on at 0700 h. They were allowed ad lib access to food (Harlan Teklad, Madison, WI) and water, except where otherwise noted.

2.2. Catheter Construction and Surgical Procedures

2.2.1. Self-administration catheter—Intra-jugular catheters were custom-made in our laboratory as described by Grigson and Twining (2002) and Twining et al. (2009).

2.2.2. Catheter and EEG/EMG electrode implantation—Rats were anesthetized and catheters were implanted into the jugular vein, as described by Grigson and Twining (2002) and Twining et al. (2009). Immediately thereafter, EEG and EMG recording electrodes were implanted as described by Fang and Fishbein (1996). Briefly, four stainless steel electrodes were implanted in the frontal and parietal bones for EEG recording, and three EMG recording electrodes made of stainless steel wire were inserted into the dorsal muscle of the neck. The electrodes and attached wires were fixed to the skull with dental cement. Following surgery, rats were allowed at least two weeks to recover. General maintenance of catheter patency involved daily examination and flushing of catheters with heparinized saline (0.2 ml of 30 IU/ml heparin). Catheter patency was verified, as needed, using 0.2 ml of propofol (Diprivan 1%) administered intravenously.

2.3. Chronic Sleep Restriction Apparatus

Chronic sleep restriction was conducted in special chambers that implement a modification of the treadmill method (the disc treadmill method) developed by the Fang laboratory (Department of Psychiatry, Pennsylvania State University College of Medicine, Hershey, PA). These chambers consist of an open-top and open-bottom Plexiglas cylinder (35.0 cm in diameter and 45.0 cm high) and a chamber bottom that is attached to a bidirectional motor (see Figure 1). The cylinder is slightly suspended above the chamber bottom filled with corncob bedding (Harlan Teklad, Madison, WI), so that the two do not turn concurrently. A metal panel (37.5 cm in diameter and 5.0 cm high) is attached to the bottom of the cylinder which is suspended above and divides the chamber bottom into two equal parts. The rats can cross this panel easily and are free to occupy either side of the chamber.

2.4. Cocaine Self-Administration Apparatus

Each rat was trained in one of twelve identical operant chambers (MED Associates, St. Albans, VT) described by Puhl et al. (2009), Puhl et al., (2011), Puhl et al. (2012). Each chamber measured 30.5 cm in length, 24.0 cm in width, and 29.0 cm in height, and was individually housed in a light- and sound-attenuated cubicle. The chambers consisted of a clear Plexiglas top, front, and back wall. The side walls were made of aluminum. Grid floors consisted of nineteen 4.8-mm stainless steel rods, spaced 1.6 cm apart (center to center). Each chamber was equipped with three retractable sipper spouts that entered through 1.3-cm diameter holes, spaced 16.4 cm apart (center to center). A stimulus light was located 6.0 cm above each tube. Each chamber also was equipped with a houselight (25 W), a tone generator (Sonalert Time Generator, 2900 Hz, Mallory, Indianapolis, IN), and a speaker for white noise (75 dB). Cocaine reinforcement was controlled by a lickometer circuit that monitored empty spout licking to operate a syringe pump (Model A, Razel Scientific Instruments, Stamford, CT). A coupling assembly attached the syringe pump to the catheter assembly on the back of each rat and entered through a 5.0-cm diameter hole in the top of the chamber. This assembly consisted of a metal spring attached to a metal spacer with Tygon tubing inserted down the center, protecting passage of the tubing from rat interference. The tubing was attached to a counterbalanced swivel assembly (Instech, Plymouth Meeting, PA) that, in turn, was attached to the syringe pump. Events in the chamber and collection of data were controlled on-line with a Pentium computer that used programs written in the Medstate notation language (MED Associates).

2.5. Drug Preparation

As described previously, individual 20-ml syringes were prepared for each self-administration chamber prior to each daily session by diluting 4.0 ml of cocaine HCl stock solution (1.24 g cocaine HCl + 150 ml saline) with 16.0 ml of heparinized saline (0.1 ml 1000 IU heparin/60.0 ml saline) for a dose of 0.33 mg/infusion (Grigson and Twining, 2002; Puhl et al., 2009; Twining et al., 2009; Wheeler et al., 2008).

2.6. Data Collection

Chronic sleep restriction, habituation training, self-administration training, and progressive ratio testing were conducted during the light phase of the light/dark cycle between 0900 h and 1700 h.

2.7. Habituation Procedure and Spout Training

Prior to the beginning of the self-administration training, the rats were moved from the wire mesh cages to the chronic sleep restriction chambers (hereafter referred to as the home cage), where they remained for the duration of the study. They were then habituated to the operant chambers for 1 h/day for three days. During this time, each rat was maintained on a water-deprivation regimen in which they received 1-h daily access to water in the operant chamber from the right spout during the habituation session and 25.0 ml of water in the chronic sleep restriction chamber overnight. Thereafter, rats were returned to ad lib access to water for the duration of the experiment.

2.8. Chronic Sleep Restriction

Immediately following the three-day habituation phase, EEG and EMG thresholds for sleep were established and adjusted for each individual animal via test recordings. EEG and EMG signals were fed into Grass NeuroData (Model 15) amplifiers through cable and computer systems, amplified, filtered, digitized at 128 Hz, and saved to the hard drive under the control of a computer program, as described by Fang et al. (1997). Chronic sleep restriction occurred in two 4-day cycles, with two recovery days occurring between each cycle. The chronic sleep restriction (CSR) group (n=11) was deprived of approximately 40% of their daily sleep, approximately evenly distributed across a 24 h period. The non-sleep restriction (NSR) group (n=10), on the other hand, was not sleep-restricted and served as chamber-matched controls, as described below. The EEG and EMG signals of the rats were continuously recorded, also as described by Fang et al. (1997). The entire sleep restriction period was divided into multiple 120-min blocks. CSR rats were allowed to sleep for 60% of their light phase baseline sleep time and 20% of their dark phase baseline sleep time. EEG and EMG information were computed and updated every two seconds. Once the computer program detected the onset of non-rapid eye movement (NREM) sleep (high amplitude EEG and low amplitude EMG) in a CSR rat, the chamber bottom rotated (one-second pulses every two seconds at a rate of 6.0 RPM) until the rat awakened. Rats were awakened as they felt the rotation of the chamber bottom or as they came in contact with the metal panel attached to the suspended cylinder of the chamber. The total number of times the motor turned on was matched between the CSR and control (i.e., NSR) groups. For the control rats, the same number of rotations of the chamber bottoms was dispersed throughout the last 12 min of each 120-min recording block, providing ample time for sleep. The results of chronic sleep restriction were verified by visual scoring of sleep stages in 10-sec segments and EEG power spectra were calculated, both as described previously (Fang and Fishbein, 1996; Fang et al., 1997).

2.9. Self-Administration Training Procedure

Self-administration training began immediately following the three-day habituation phase, and was conducted concurrently with chronic sleep restriction. Each rat was trained during three daily 90-min FR sessions, followed by one PR test day and two recovery days. This six-day cycle was then repeated. See Figure 2 for a timeline of behavioral training and experimental testing. Specifically, rats were placed in operant chambers in darkness.

Immediately upon initiation of the 90-min FR session, the white noise was turned on, two empty spouts advanced into the chamber, and the cue light above the active spout was illuminated. The right spout was termed the “active” spout, while the left spout was termed the “inactive” spout. A FR5 schedule of reinforcement was implemented. During this time, completion of 5 licks on the “active” spout was followed by a single intravenous (i.v.) infusion of 0.33 mg cocaine over six seconds. Drug delivery was signaled by offset of the stimulus light, retraction of the “active” spout, and onset of the tone and houselight. The tone and houselight remained on for a 20-sec timeout period. Responding on the “inactive” spout was without consequence throughout each session. Following each self-administration training session, the rats were returned to their home cages. There were three such sessions in each six-day cycle.

2.10. Progressive Ratio Testing

Fixed ratio training was followed by PR testing to examine the impact of chronic sleep restriction on the rats’ willingness to work for drug. Thus, following the third day of FR training in each training block, PR testing was conducted (see Figure 2) as described by Puhl et al. (2009) and Puhl et al. (2012). During PR testing, rats were placed in the operant chambers with conditions identical to those of self-administration training, except the number of active responses required to receive each infusion progressively increased by a multiple of five for up to ten infusions (1, 1+5=6, 6+10=16, 16+15=31, 31+20=51, 51+25=76, 76+30=106, 106+35=141, 141+40=181, 181+45=226). Thereafter, the number of responses required for each successive infusion increased by 50 (226+50=276, 276+50=326, 326+50=376, etc.). During this PR session, rats were allowed to self-administer cocaine (0.33 mg/infusion) until a period of 30 min elapsed without receipt of an infusion. Break point (the highest ratio completed) was measured.

2.11. Data Analysis

All data were analyzed with Statistica (Version 9, StatSoft, Tulsa, OK) and Prism (Version 5, GraphPad, San Diego, CA) using one-way and mixed factorial analysis of variance (ANOVA) tests. Newman-Keuls and Bonferroni post hoc tests were conducted on significant ANOVAs, when appropriate, with α set at 0.05. In addition, Student’s t-tests were conducted when appropriate.

3. Results

3.1. Replication

We observed no statistically significant effect of replication in any of the variables measured ($F_s < 1$).

3.2. Chronic Sleep Restriction

3.2.1. Time spent in wakefulness, NREM sleep, and REM sleep—Time spent in wakefulness, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep was analyzed during the single baseline recording day and during the six complete 24-hr recording days concurrent with self-administration training using three separate 2×2

mixed factorial ANOVAs varying sleep restriction group (NSR or CSR) and recording period (baseline or training). Analysis of time spent in wakefulness revealed significant main effects of group, $F(1, 19)=7.33$, $p < 0.02$, and recording period, $F(1, 19)=36.22$, $p < 0.01$, indicating that, overall, CSR rats exhibited more wakefulness than NSR rats and that wakefulness, in general, was greater during self-administration training than during baseline recording. In addition, a significant group $\times$ recording period interaction was found, $F(1, 19)=24.73$, $p < 0.01$. Post hoc tests of this two-way interaction revealed that the amount of time spent in wakefulness did not differ between NSR and CSR rats during baseline recording ($p > 0.05$; see Figure 3, left panel). Also, the amount of time spent in wakefulness did not differ between baseline recording and self-administration training among NSR rats ($p > 0.05$). However, CSR rats spent more time in wakefulness during self-administration training than during baseline recording ($p < 0.01$) and they spent more time in wakefulness during self-administration training than did the NSR controls ($p < 0.01$; see Figure 3, right panel).

Analysis of time spent in NREM sleep also revealed significant main effects of group, $F(1, 19)=6.38$, $p < 0.03$, and recording period, $F(1, 19)=46.07$, $p < 0.01$, indicating that, overall, CSR rats exhibited less NREM sleep than NSR rats and that less time was spent in NREM sleep during self-administration training than baseline recording. In addition, a significant group $\times$ recording period interaction was found, $F(1, 19)=26.37$, $p < 0.01$. Post hoc tests of this two-way interaction revealed a pattern mirroring that described for wakefulness. The amount of time spent in NREM sleep did not differ between NSR and CSR rats during baseline recording ($p > 0.05$; see Figure 3, left panel). The amount of time spent in NREM sleep also did not differ between baseline recording and self-administration training among NSR rats ($p > 0.05$). However, CSR rats spent less time in NREM sleep during self-administration training than baseline recording ($p < 0.01$) and also spent less time in NREM sleep during self-administration training than did their NSR counterparts ($p < 0.01$; see Figure 3, right panel).

Finally, analysis of time spent in REM sleep failed to reveal a significant main effect of group, $F(1, 19)=1.59$, $p > 0.05$, but did reveal a significant main effect of recording period, $F(1, 19)=4.51$, $p < 0.05$, indicating that, overall, less time was spent in REM sleep during self-administration training than baseline recording. Post hoc tests of a significant group $\times$ recording period interaction, $F(1, 19)=12.09$, $p < 0.01$, found that the amount of time spent in REM sleep did not differ between NSR and CSR rats during baseline recording ($p > 0.05$; see Figure 3). Also, the amount of time spent in REM sleep did not differ between baseline recording and self-administration training among NSR rats ($p > 0.05$). However, CSR rats spent less time in REM sleep during self-administration training than during baseline recording ($p < 0.01$) and also spent less time in REM sleep than NSR rats during self-administration training ($p < 0.02$; see Figure 3, right panel). Together, these data show that CSR rats were chronically sleep-deprived during self-administration training, while the NSR control rats were not.

3.2.2. Cumulative time differences in wakefulness and NREM sleep—In

addition, the cumulative time differences in wakefulness, NREM sleep, and REM sleep between baseline recording and the six complete 24-hr recording days during self-administration training were calculated. The two PR test days were not included given that chronic sleep restriction and EEG/EMG recording were terminated immediately following each PR session. Also, the two-day recovery period was not included given that chronic sleep restriction was not conducted and EEG/EMG recording was suspended. One-way ANOVAs revealed that CSR rats spent significantly more time in wakefulness, significantly less time in NREM sleep, and significantly less time in REM sleep across self-administration training days than NSR rats ($ps < 0.01$; see Figure 4). These data indicate that

CSR rats cumulatively lost over 16 h of NREM sleep and nearly 4 h of REM sleep throughout self-administration training (i.e., CSR rats experienced approximately a 40% reduction in total sleep time during self-administration training).

3.3. Cocaine Self-Administration

3.3.1. Fixed ratio training—Consistent with previous reports from our laboratory (Grigson and Twining, 2002; Puhl et al., 2009; Puhl et al., 2012; Twining et al., 2009), two subpopulations of rats were identified following FR self-administration training: low drug-takers (NSR: $n=6$; CSR $n=5$) and high-drug-takers (NSR $n=4$; CSR $n=6$). These groups were separated, as described previously, by calculating the mean number of infusions self-administered during terminal FR training (FR trials 4-6) and then choosing the clearest group division point among the means (Grigson and Twining, 2002; Puhl et al., 2012; Twining et al., 2009). All rats that self-administered a mean of 10 infusions or more were defined as high drug-takers, while those that self-administered less than 10 infusions were defined as low drug-takers. Although CSR high drug-takers tended to self-administer more infusions than NSR high-drug-takers during FR training, a 2×2 factorial ANOVA varying sleep restriction group (NSR or CSR) and drug-taking group (low or high) showed no significant effect of sleep restriction group, $F(1, 17)=1.97$, $p=0.18$, during terminal FR training (FR trials 4-6; see Figure 5). However, there was a significant main effect of drug-taking group, $F(1, 17)=66.61$, $p < 0.01$, indicating that, overall, high drug-takers self-administered more cocaine infusions than low drug-takers during terminal FR training. The sleep restriction group $\times$ drug-taking group interaction, however, was not significant, $F(1, 17)=0.91$, $p=0.35$.

In addition, separate 2×6 factorial ANOVAs varying spout response (active or inactive) and FR trial (1-6) were conducted on low and high drug-takers in the NSR and CSR groups. For low drug-taking rats in the NSR group, there was no significant effect of spout response, $F(1, 1)=0.63$, $p > 0.05$, but there was a significant effect of FR trial, $F(1, 5)=2.62$, $p < 0.05$, indicating that, overall, responding decreased as FR training progressed (see Figure 6, left panel). For high drug-taking rats in the NSR group, there were neither significant effects of spout response, $F(1, 1)=4.19$, $p > 0.05$, nor FR trial, $F(1, 5)=0.73$, $p > 0.05$ (see Figure 6, right panel). Likewise, there were no significant effects for spout response, $F(1, 1)=0.001$, $p > 0.05$, or FR trial, $F(1, 5)=1.55$, $p > 0.05$, for low drug-taking rats in the CSR group (see Figure 7, left panel). However, there were significant effects of both spout response, $F(1, 1)=13.16$, $p < 0.05$, and FR trial, $F(1, 5)=3.25$, $p < 0.05$, for high drug-taking rats in the CSR group (see Figure 7, right panel). Post-hoc tests indicated that responses on the active spout were significantly higher than responses on the inactive spout during FR trials 4-6, $ps < 0.05$. Together, these results indicate that the facilitative effects of chronic sleep restriction are limited to high drug-taking rats and that those effects appear as early as the fourth day of FR self-administration training.

3.3.2. Progressive ratio testing—A similar 2×2 factorial ANOVA varying sleep restriction group (NSR or CSR) and drug-taking group (low or high) was conducted on PR breakpoint. This analysis revealed significant main effects of sleep restriction group, $F(1, 17)=4.76$, $p < 0.05$, and drug-taking group, $F(1, 17)=7.43$, $p < 0.02$ (data not shown) across both PR test sessions. The sleep restriction group $\times$ drug-taking group interaction approached statistical significance, $F(1,17)=3.89$, $p=0.06$, and post hoc tests revealed that, while NSR low and high drug-takers did not differ from one another, CSR high drug-takers exhibited significantly higher breakpoints than CSR low drug-takers ($p < 0.02$), as well as all other groups ($p < 0.02$). Additionally, Student's *t*-tests were used to compare cocaine infusions self-administered during individual PR tests by low and high-drug taking rats in the NSR and CSR groups. While there were no statistically significant differences between

NSR low and high drug-takers on either PR test ($p > 0.05$; see Figure 8, left panel), infusions self-administered by CSR high drug-takers nearly reached statistical significance compared to CSR low drug-takers during the first PR test ($p = 0.06$) and were significantly higher during the second PR test ($p < 0.05$; see Figure 8, right panel). These results indicate that CSR high drug-taking rats were willing to work harder for drug early during the acquisition of self-administration than were their NSR counterparts.

4. Discussion

In a previous study, we showed that acute sleep deprivation of just 4-8 hours significantly increased goal-directed behavior and the rate of responding for cocaine in drug-experienced rats tested on a PR schedule of reinforcement (Puhl et al., 2009). Here, we were able to evaluate the effects of chronic sleep restriction (more akin to the type of sleep deprivation experienced by humans) imposed early during acquisition of cocaine self-administration. As such, this is the first animal model to directly investigate the effects of chronic sleep deprivation (indeed, any sleep deprivation) on the acquisition of drug-seeking and drug-taking behaviors and on the willingness to work for drug. The results showed that chronic sleep restriction (approximately 40% sleep loss over the course of eight days separated by a two-day recovery period) increased FR responding for cocaine by the fourth day of self-administration training and greatly enhanced responding for cocaine on a PR schedule of reinforcement. These findings suggest that even a relatively short period of chronic sleep deprivation can augment the perceived incentive value of cocaine in relatively inexperienced high drug-taking rats. However, the performance of low drug-taking rats was not affected.

While novel, these results are not completely surprising given the clinical literature (Brower, 2001; Clark et al., 1998; Foster and Peters, 1999; Gillin et al., 1994; Roehrs et al., 1999, 2004) and the known neurochemical consequences of sleep deprivation. For instance, sleep deprivation has been shown to augment dopamine (DA) activity in the mesocorticolimbic reward system (Asakura et al., 1992; Brock et al., 1995; Farooqui et al., 1996; Hernández-Peón et al., 1969). This augmentation is indicated by increases in DA levels (Hernández-Peón et al., 1969), increases in DA metabolite levels (Asakura et al., 1992; Farooqui et al., 1996), increases in DA receptor densities (Brock et al., 1995; Demontis et al., 1990; Hamdi et al., 1993), and decreases in the affinity for DA at reuptake sites (Hamdi et al., 1993). Accordingly, sleep deprivation also has been shown to increase sensitivity to DA agonists (Nunes et al., 1994; Tufik, 1981). Along with the current data, these studies suggest that, among other possible mechanisms, sleep deprivation may augment the perceived reward value of cocaine by enhancing and prolonging the effects of DA in the brain's reward circuit. However, if sleep deprivation is not affecting drug-seeking and drug-taking behaviors directly via the mesocorticolimbic DA system, an alternative neural substrate for the effects shown here is the HPA axis, as sleep deprivation is a potent stressor that has been shown to cause an increase in corticosterone (España and Scammell, 2004) and corticotropin releasing factor (CRF), which initiates activation of the HPA axis, plays a prominent role in the neurobiology of addiction (see Corominas et al., 2010 for a review). Quite interestingly, whatever the mechanisms, these effects are, as stated, only evident in high drug-taking rats.

Here we focused on acquisition of cocaine self-administration, as it is during initial exposure to the drug that the reward system is particularly malleable, and changes in the reward circuitry that occur during this critical period are capable of altering responding for drug over extended periods of time. Differences in several neural substrates have been identified during acquisition of drug self-administration compared to expression of drug-seeking and drug-taking behaviors (see Stuber et al., 2010 for a review). For example, expression of serotonin (5-HT)_{1B} receptors in the dorsal striatum was shown to be upregulated during acquisition of cocaine self-administration (Neumaier et al., 2009) and administration of the

dopamine antagonist α -flupenthixol attenuated responding for cocaine early in acquisition when infused into the dorsomedial striatum, but decreased responding for cocaine when infused into the dorsolateral striatum after self-administration had been established (Murray et al., 2012). It is possible, then, that chronic sleep restriction is interacting with similar neural substrates early during acquisition, resulting in the augmentation of the perceived reward value to cocaine shown in this study.

It remains to be seen whether these results can be generalized to natural rewards (e.g., saccharin or sucrose), which also engage the mesocorticolimbic DA system (Bello et al., 2002; Bello et al., 2003; Hajnal and Norgren, 2002; Roop et al., 2002). In support of such a possibility, acute sleep deprivation has been shown to enhance the response of the anterior cingulate cortex to images of food, and activation was correlated with subjective measures of appetite (Benedict et al., 2012). Also, In addition, obesity has recently been linked to disrupted sleep patterns in adolescents (Shaikh et al., 2009) and adults (Adámková et al., 2009; Cizza et al., 2010) and we have demonstrated that rats with a history of having binged on fat are more likely to demonstrate addiction-like behavior for cocaine (Puhl et al., 2011). Thus, chronic sleep deprivation may augment the perceived reward value of food as well as drug, and responding for the two may, in some cases, be intertwined.

Admittedly, the current study employed a relatively easy FR schedule of reinforcement (four times lower than the terminal schedule employed during our acute sleep deprivation study). As such, it could be argued that the results obtained were a function of the ease of acquiring drug. However, this explanation seems unlikely due to the fact that, during PR testing, high drug-taking rats in the CSR group were, on average, making nearly 400 responses to receive a single cocaine infusion, with some rats making well over 1000 responses for a single infusion. This finding indicates that they were very willing to work for drug even when an exceptionally large number of responses was required.

In addition, it is possible that low drug-takers are simply more sensitive to sleep deprivation and, as such, were unable to respond for cocaine due to excessive fatigue. In support of this alternative, differences in sleep patterns have been demonstrated among low and high responders in the locomotor activity task, a well known method for identifying high drug-takers *a priori* (Hooks, et al., 1991; Piazza et al., 1989; Piazza et al., 2000). Specifically, low responders in the locomotor activity task (i.e., those likely to be low drug-takers) exhibited greater amounts of slow wave sleep and less wakefulness compared to high responders (Bouyer et al., 1998). However, this possibility also seems unlikely for several reasons. First, the amount of sleep deprivation imposed, although chronic, was fairly modest. Second, this explanation seems implausible given the activating effects of acute sleep deprivation on low drug-takers that we have demonstrated previously (Puhl et al., 2009). Furthermore, we have shown previously that although low drug-takers self-administer extremely low levels of cocaine during FR training, when extinction training was instituted (i.e., when responding on the “active” spout was no longer reinforced with cocaine infusions) low drug-takers exhibited levels of responding on the “active” spout that were comparable to those of high drug-takers (Puhl et al., 2009). This indicates that low drug-takers are, in fact, motivated to self-administer cocaine, but simply at a lower level than high drug-takers. Finally, the results shown by Bouyer et al. (1998) are open to two opposing interpretations. First, increased slow wave sleep among low drug-takers could make them more susceptible to sleep deprivation given a need for more sleep at baseline. However, it also could make them less sensitive to sleep deprivation given their already high levels of baseline sleep. In addition, a recent human study showed that global poor sleep quality is associated with increased negative consequences of alcohol consumption, specifically among heavy drinkers (Kenney et al., 2012), which suggests, along with the data presented here, that, if anything, high drug-takers may be more vulnerable to the effects of sleep deprivation on drug-taking behavior.

In summary, these findings, in conjunction with previous work (Puhl et al., 2009), suggest that sleep deprivation augments the perceived incentive reward value of cocaine and, consequently, the drive to self-administer cocaine. Thus, the facilitative effect of chronic sleep deprivation was evident both during FR responding and when rats were challenged to work for drug on a PR schedule of reinforcement. Low drug-takers were seemingly impervious to this manipulation, while high drug-takers were the most vulnerable. With substance abuse and sleep deprivation rampant in our society, these results have important implications for the prevention and treatment of addiction in humans. This is the first study to directly investigate the behavioral influences of chronic sleep deprivation on the acquisition of drug self-administration behavior and the willingness to work for drug. As such, it offers a valuable animal model that can be used to further investigate the effects of chronic sleep restriction on drug-seeking and drug-taking behaviors and to identify the underlying neural mechanisms involved. Indeed, while we now know something of the effect of chronic sleep restriction on the acquisition of cocaine self-administration, future studies must determine how chronic sleep restriction affects the acquisition of self-administration of other drugs of abuse or, importantly, maintenance and reinstatement of drug seeking and drug taking in drug-experienced rats. In addition, we also must more fully characterize the effects of chronic sleep restriction on the intake of natural rewards (e.g., saccharin, sucrose, and fat), given that the link between poor sleep and obesity is beginning to be explored in humans. Finally, recent evidence suggests that sleep problems in adolescence can predict substance abuse (Wong et al., 2010), and, in fact, shifts in sleep timing in adolescents have been shown to result in decreased activation of areas of the brain related to reward processing (specifically, the medial prefrontal cortex and striatum) in response to monetary rewards, which is thought to indicate a reduction in reward sensitivity (Hasler et al., 2012). Given the prevalence of chronic sleep deprivation in the adolescent population (Carskadon, 1990; Eaton et al., 2010) and their known sensitivity to drugs of abuse (Johnston et al., 2008a; Johnston et al., 2008b), future studies also must examine the impact of chronic sleep deprivation on both acquisition and reinstatement of drug-seeking and drug-taking behavior in the adolescent rat.

Acknowledgments

The authors would like to thank the National Institute on Drug Abuse for generously supplying the cocaine HCl used in this study. This work was supported by grants DA009815 and DA023315 from the National Institutes of Health.

References

- Adámková V, Hubáček JA, Lánská V, Vrablík M, Králová Lesná I, Suchánek P, Zimmerlová P, Veleminský M. Association between duration of sleep and body weight. *Physiol Res.* 2009; 58(Suppl 1):S27–S31. [PubMed: 19857033]
- Asakura W, Matsumoto K, Ohta H, Watanabe H. REM sleep deprivation decreases apomorphine-induced stimulation of locomotor activity but not stereotyped behavior in mice. *Gen Pharmacol.* 1992; 23(3):337–341. [PubMed: 1511844]
- Bello NT, Lucas LR, Hajnal A. Repeated sucrose access influences dopamine D2 receptor density in the striatum. *Neuroreport.* 2002; 13(12):1575–1578. [PubMed: 12218708]
- Bello NT, Sweigart KL, Lakoski JM, Norgren R, Hajnal A. Restricted feeding with scheduled sucrose access results in an upregulation of the rat dopamine transporter. *Am J Physiol Regul Integr Comp Physiol.* 2003; 284(5):R1260–R1268. [PubMed: 12521926]
- Benedict C, Brooks SJ, O'Daly OG, Almén MS, Morell A, Åberg K, Gingnell M, Schultes B, Hallschmid M, Broman J, Larsson E, Schiöth HB. Acute sleep deprivation enhances the brain's response to hedonic food stimuli: An fMRI study. *J Clin Endocrinol Metab.* 2012; 97(3):E443–E447. [PubMed: 22259064]

- Bouyer JJ, Vallée M, Deminière JM, Le Moal M, Mayo W. Reaction of sleep- wakefulness cycle to stress is related to differences in hypothalamo-pituitary-adrenal axis reactivity in rat. *Brain Res.* 1998; 804(1):114–124. [PubMed: 9729321]
- Brock JW, Hamdi A, Ross K, Payne S, Prasad C. REM sleep deprivation alters dopamine D₂ receptor binding in the rat frontal cortex. *Pharmacol Biochem Behav.* 1995; 52(1):43–48. [PubMed: 7501677]
- Brower KJ. Alcohol's effects on sleep in alcoholics. *Alcohol Res Health.* 2001; 25(2):110–125. [PubMed: 11584550]
- Carskadon MA. Patterns of sleep and sleepiness in adolescents. *Pediatrician.* 1990; 17(1):5–12. [PubMed: 2315238]
- Ciccocioppo R, Martin-Fardon R, Weiss F. Stimuli associated with a single cocaine experience elicit long-lasting cocaine-seeking. *Nat Neurosci.* 2004; 7(5):495–6. [PubMed: 15048121]
- Cizza G, Marincola P, Mattingly M, Williams L, Mitler M, Skarulis M, Csako G. Treatment of obesity with extension of sleep duration: A randomized, prospective, controlled trial. *Clin Trials.* 2010; 7(3):274–285. [PubMed: 20423926]
- Clark CP, Gillin JC, Golshan S, Demodena A, Smith TL, Danowski S, Irwin M, Schuckit M. Increased REM sleep density at admission predicts relapse by three months in primary alcoholics with a lifetime diagnosis of secondary depression. *Biol Psychiatry.* 1998; 43(8):601–607. [PubMed: 9564445]
- Corominas M, Roncero C, Casas M. Corticotropin releasing factor and neuroplasticity in cocaine addiction. *Life Sci.* 2010; 86(1-2):1–9. [PubMed: 19914260]
- DeJong W. Relapse prevention: An emerging technology for promoting long-term abstinence. *Int J Addict.* 1994; 29(6):681–705. [PubMed: 8034380]
- Demontis MG, Fadda P, Devoto P, Martellotta MC, Fratta W. Sleep deprivation increases dopamine D₁ receptor antagonist [³H]SCG 23390 binding and dopamine-stimulated adenylate cyclase in the rat limbic system. *Neurosci Lett.* 1990; 117(1-2):224–227. [PubMed: 2149748]
- Eaton DK, McKnight-Eily LR, Lowry R, Perry GS, Presley-Cantrell L, Croft JB. Prevalence of insufficient, borderline, and optimal hours of sleep among high school students. *J Adolesc Health.* 2010; 46(4):399–401. [PubMed: 20307832]
- España RA, Scammell TE. Sleep neurobiology for the clinician. *Sleep.* 2004; 27(4):811–820. [PubMed: 15283019]
- Fang J, Fishbein W. Sex differences in paradoxical sleep: Influences of estrus cycle and ovariectomy. *Brain Res.* 1996; 734(1-2):275–285. [PubMed: 8896835]
- Fang J, Wang Y, Krueger JM. Mice lacking the TNF 55 kDa receptor fail to sleep more after TNF α treatment. *J Neurosci.* 1997; 17(15):5949–5955. [PubMed: 9221791]
- Farooqui SM, Brock JW, Zhou J. Changes in monoamines and their metabolite concentrations in REM sleep-deprived rat forebrain nuclei. *Pharmacol Biochem Behav.* 1996; 54(2):385–391. [PubMed: 8743599]
- Foster JH, Peters TJ. Impaired sleep in alcohol misusers and dependent alcoholics and the impact upon outcome. *Alcohol Clin Exp Res.* 1999; 23(6):1044–1051. [PubMed: 10397289]
- Gillin JC, Smith TL, Irwin M, Butters N, Demodena A, Schuckit M. Increased pressure for rapid eye movement sleep at time of hospital admission predicts relapse in nondepressed patients with primary alcoholism at 3-month follow-up. *Arch Gen Psychiatry.* 1994; 51(3):189–197. [PubMed: 8122956]
- Gillin, JC.; Drummond, SPA. Medication and substance abuse. In: Kryger, MH.; Roth, T.; Dement, WC., editors. *Principles and Practice of Sleep Medicine*. Saunders; Philadelphia: 2000. p. 1176-1195.
- Grigson PS, Twining RC. Cocaine-induced suppression of saccharin intake: A model of drug-induced devaluation of natural rewards. *Behav Neurosci.* 2002; 116(2):321–333. [PubMed: 11996317]
- Hajnal A, Norgren R. Repeated access to sucrose augments dopamine turnover in the nucleus accumbens. *Neuroreport.* 2002; 13(17):2213–2216. [PubMed: 12488799]
- Hale L, Do DP. Racial differences in self-reports of sleep duration in a population-based study. *Sleep.* 2007; 30(9):1096–1103. [PubMed: 17910381]

- Hamdi A, Brock J, Ross K, Prasad C. Effects of rapid eye movement sleep deprivation on the properties of striatal dopaminergic system. *Pharmacol Biochem Behav.* 1993; 46(4):863–866. [PubMed: 7906037]
- Hasler BP, Dahl RE, Holm SM, Jakubcak JL, Ryan ND, Silk JS, Phillips ML, Forbes EE. Weekend-weekday advances in sleep timing are associated with altered reward-related brain function in healthy adolescents. *Biol Psychol.* 2012; 91(3):334–341. [PubMed: 22960270]
- Hernández-Peón R, Drucker RR, Del Angel AR, Chavez B, Serrano P. Brain catecholamines and serotonin in rapid sleep deprivation. *Physiol Behav.* 1969; 4(4):659–661.
- Hooks MS, Jones GH, Smith AD, Neill DB, Justice JB Jr. Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. *Synapse.* 1991; 9(2):121–128. [PubMed: 1821483]
- Jean-Louis G, Kripke DF, Ancoli-Israel S. Sleep and quality of well-being. *Sleep.* 2000; 23(8):1115–1121. [PubMed: 11145326]
- Johnston, LD.; O'Malley, PM.; Bachman, JG.; Schulenberg, JE. Secondary School Students. Vol. I. National Institute on Drug Abuse; Bethesda, MD: 2008a. Monitoring the Future: National Survey Results on Drug Use, 1975–2002.
- Johnston, LD.; O'Malley, PM.; Bachman, JG.; Schulenberg, JE. College Students and Adults Ages 19–45. Vol. II. National Institute on Drug Abuse; Bethesda, MD: 2008b. Monitoring the Future: National Survey Results on Drug Use, 1975–2002.
- Kenney SR, LaBrie JW, Hummer JF, Pham AT. Global sleep quality as a moderator of alcohol consumption and consequences in college students. *Addict Behav.* 2012; 37(4):507–512. [PubMed: 22285119]
- Murray JE, Belin D, Everitt BJ. Double dissociation of the dorsomedial and dorsolateral striatal control over the acquisition and performance of cocaine seeking. *Neuropsychopharmacology.* 2012; 37(11):2456–2466. [PubMed: 22739470]
- National Institute on Drug Abuse. [April 26, 2012] <http://www.nida.nih.gov>
- National Sleep Foundation. [April 26, 2012] <http://www.sleepfoundation.org>
- Neumaier JF, McDevitt RA, Polis IY, Parsons LH. Acquisition of and withdrawal from cocaine self-administration regulates 5-HT mRNA expression in rat striatum. *J Neurochem.* 2009; 111(1):217–227. [PubMed: 19659573]
- Nunes GP, Tufik S, Nobrega JN. Autoradiographic analysis of D₁ and D₂ dopaminergic receptors in rat brain after paradoxical sleep deprivation. *Brain Res Bull.* 1994; 34(5):453–456. [PubMed: 8082038]
- O'Brien, CP. Drug addiction and drug dependence. In: Hardman, JG.; Limbird, LE.; Gilman, AG., editors. Goodman and Gilman's: The pharmacological basis of therapeutics. 10. McGraw Hill; New York: 2001. p. 622
- Piazza PV, Deminière J, Le Moal M, Simon H. Factors that predict individual vulnerability to amphetamine self-administration. *Science.* 1989; 245(4925):1511–1513. [PubMed: 2781295]
- Piazza PV, Deroche-Gamonet V, Rouge-Pont F, Le Moal M. Vertical shifts in self-administration dose-response functions predict a drug-vulnerability phenotype predisposed to addiction. *J Neurosci.* 2000; 20(11):4226–4232. [PubMed: 10818158]
- Puhl MD, Blum JS, Acosta-Torres S, Grigson PS. Environmental enrichment protects against the acquisition of cocaine taking and seeking in adult male rats, but does not attenuate avoidance of a drug-associated saccharin cue. *Behav Pharmacol.* 2012; 23(1):43–53. [PubMed: 22157144]
- Puhl MD, Cason AM, Wojnicki FHE, Corwin RL, Grigson PS. A history of bingeing on fat enhances cocaine seeking and taking. *Behav Neurosci.* 2011; 125(6):930–942. [PubMed: 21988520]
- Puhl MD, Fang J, Grigson PS. Acute sleep deprivation increases the rate and efficiency of cocaine self-administration, but not the perceived value of cocaine in rats. *Pharmacol Biochem Behav.* 2009; 94(2):262–270. [PubMed: 19751755]
- Roehrs T, Johanson CE, Meixner R, Turner L, Roth T. Reinforcing and subjective effects of mthylphenidate: Dose and time in bed. *Exp Clin Psychopharmacol.* 2004; 12(3):180–189. [PubMed: 15301635]
- Roehrs T, Papineau K, Rosenthal L, Roth T. Sleepiness and the reinforcing and subjective effects of methylphenidate. *Exp Clin Psychopharmacol.* 1999; 7(2):145–150.

- Roop RG, Hollander JA, Carelli RM. Accumbens activity during a multiple schedule for water and sucrose reinforcement in rats. *Synapse*. 2002; 43(4):223–226. [PubMed: 11835516]
- Shaikh WA, Patel M, Singh S. Sleep deprivation predisposes gujarati Indian adolescents to obesity. *Indian J Community Med*. 2009; 34(3):192–194. [PubMed: 20049294]
- Stuber GD, Hopf FW, Tye KM, Chen BT, Bonci A. Neuroplastic alterations in the limbic system following cocaine or alcohol exposure. *Curr Top Behav Neurosci*. 2010; 3:3–27. [PubMed: 21161748]
- Tufik S. Changes of response to dopaminergic drugs in rats submitted to REM-sleep deprivation. *Psychopharmacology (Berl)*. 1981; 72(3):257–260. [PubMed: 6111823]
- Twining RC, Bolan M, Grigson PS. Yoked delivery of cocaine is aversive and protects against the motivation for drug in rats. *Behav Neurosci*. 2009; 123(4):913–925. [PubMed: 19634952]
- Wheeler RA, Twining RC, Jones JL, Slater JM, Grigson PS, Carelli RM. Behavioral and electrophysiological indices of negative affect predict cocaine self-administration. *Neuron*. 2008; 57(5):774–785. [PubMed: 18341996]
- Wong MM, Brower KJ, Nigg JT, Zucker RA. Childhood sleep problems, response inhibition, and alcohol and drug outcomes in adolescence and young adulthood. *Alcohol Clin Exp Res*. 2010; 34(6):1033–1044. [PubMed: 20374209]

Highlights

- Rats were trained to self-administer cocaine.
- Rats were subjected to chronic sleep restriction using the disc treadmill method.
- Chronic sleep restriction occurred early during acquisition of self-administration.
- The disc treadmill method is a novel and effective model of chronic sleep restriction.
- Chronic sleep restriction increased FR responding and PR breakpoint in high drug-takers only.
- These results have important clinical implications for addiction and relapse.

Figure 1.
Disc treadmill apparatus for chronic sleep restriction.

Figure 2. Timeline of behavioral training and experimental testing. Chronic sleep restriction was imposed concurrently with FR training and PR testing in two blocks separated by two recovery days.

Figure 3.

Mean ($\pm$ SEM) time spent in wakefulness, NREM sleep, and REM sleep. *Left panel.* Mean ($\pm$ SEM) time spent in wakefulness, NREM sleep, and REM sleep during baseline recording. White bars represent wakefulness, gray bars represent NREM sleep, and black bars represent REM sleep. *Right panel.* Mean ($\pm$ SEM) time spent in wakefulness, NREM sleep, and REM sleep during the six complete days of 24-hr recording during self-administration training. White bars represent wakefulness, gray bars represent NREM sleep, and black bars represent REM sleep. * denotes statistical significance ($p < 0.02$) between the NSR and CSR group during self-administration training. # denotes statistical significance ($p < 0.01$) for the CSR group between baseline and self-administration training.

Figure 4.

Mean (+/- SEM) cumulative differences in time spent in wakefulness, NREM sleep, and REM sleep between baseline recording and the six complete 24-h recording days during self-administration training in NSR (left panel) and CSR (right panel) rats. White bars represent wakefulness, gray bars represent NREM sleep, and black bars represent REM sleep. * denotes statistical significance ($p < 0.01$) between the NSR and CSR group.

Figure 5. Mean ($\pm$ SEM) cocaine infusions self-administered during terminal fixed ratio (FR) training (FR trials 4-6). White bars represent the NSR group and gray bars represent the CSR group.

Figure 6.

Mean ($\pm$ SEM) responses made during fixed ratio (FR) training in the NSR group. *Left panel.* Mean ($\pm$ SEM) responses made during FR training by NSR low drug-takers. Black circles represent responses made on the active spout and white circles represent responses made on the inactive spout. *Right panel.* Mean ($\pm$ SEM) responses made during FR training by NSR high drug-takers. Black circles represent responses made on the active spout and white circles represent responses made on the inactive spout.

Figure 7.

Mean (+/- SEM) responses made during fixed ratio (FR) training in the CSR group. *Left panel.* Mean (+/- SEM) responses made during FR training by CSR low drug-takers. Black circles represent responses made on the active spout and white circles represent responses made on the inactive spout. *Right panel.* Mean (+/- SEM) responses made during FR training by CSR high drug-takers. Black circles represent responses made on the active spout and white circles represent responses made on the inactive spout. * denotes statistical significance ($p_s < 0.05$) between responses made on the active spout and responses made on the inactive spout.

Figure 8.

Mean (+/- SEM) infusions self-administered during progressive ratio (PR) testing. *Left panel.* Mean (+/- SEM) infusions self-administered during PR testing in the NSR group. White bars represent low drug-takers and gray bars represent high drug-takers. *Right panel.* Mean (+/- SEM) infusions self-administered during PR testing in the CSR group. White bars represent low drug-takers and gray bars represent high drug-takers. * denotes statistical significance ($p < 0.05$) between CSR high drug-takers and CSR low drug-takers during the second PR test.