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A novel model of chronic sleep restriction reveals an increase in the perceived incentive reward value of cocaine in high drug-taking rats

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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 25% 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.

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

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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 Fig. 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, 2011, 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

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 computator 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,