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Effects of low dose cocaine on REM sleep in the freely moving rat

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Abstract

Cocaine administration can be disruptive to sleep. In compulsive cocaine users, sleep disruption may be a factor contributing to relapse. The effects of cocaine on sleep, particularly those produced by low doses, have not been extensively studied. Low dose cocaine may stimulate brain reward systems that are linked to the liability of abusing of this drug. This study was designed to assess the effects of the acute administration of low to moderate cocaine doses on sleep in the rat. Polygraphic recordings were obtained from freely moving, chronically instrumented rats over a 6-h period after the administration of either cocaine (as a 2.5–10 mg/kg intraperitoneal dose) or saline. Following cocaine administration, time spent by the rats in wakefulness increased and slow wave sleep decreased in a dose-dependent manner, compared to controls. These changes lasted between 1 to 3 h following the cocaine administration. Rapid eye movement (REM) sleep was decreased during a 2- to 3-h period following the injection of 5 and 10 mg/kg doses of cocaine. In contrast, REM sleep increased during the periods 2–4 h after the administration of 2.5 and 5 mg/kg doses of cocaine. These results indicate that sleep can be significantly altered by low doses of cocaine when administered subacutely.

Keywords

cocaine; rat; REM sleep; slow-wave sleep; wakefulness

Introduction

Sleep disturbance is a common feature associated with cocaine use and withdrawal in individuals with histories of cocaine dependence or abuse.^{1–4} These drug-induced changes in sleep patterns may have a negative influence on mood, which could be a possible factor leading to relapse. Thus, an understanding of the mechanism through which cocaine administration influences sleep may be of value in developing strategies for the management of cocaine use disorders. The acute administration of cocaine to individuals who are dependent on this drug produces a reduction in sleep efficiency and the percentage of time spent in rapid eye movement (REM) sleep.⁵ There are a few clinical studies in which sleep disturbances associated with cocaine withdrawal have been assessed using electroencephalographic techniques.^{5–8} One group of investigators found that, compared to normative values, cocaine-dependent individuals exhibited an increased percentage of REM sleep and a decreased percentage of slow-wave sleep (SWS) during withdrawal.⁶ Other investigators, however, reported that although the latency for REM sleep significantly decreased, the percentage of REM sleep did

not differ from that of age-matched controls during cocaine withdrawal.⁵ Different levels of cocaine use may explain the discrepancies in clinical findings concerning use and effects on sleep. In clinical studies, controlling the amount of cocaine used by subjects over their lifetimes as well as the amount of cocaine consumed outside laboratory settings cannot be reliably and accurately determined.

Animal studies provide a way to carefully control cocaine intake while examining the effects of cocaine on sleep in drug-naïve subjects. Only a few such studies have been conducted. Cocaine administered to rats as a 6-mg/kg intraperitoneal (i.p.) dose, when compared to the effects of vehicle, depressed total sleep time and slow wave sleep (SWS) and increased sleep latency.⁹ This dose was found to significantly decrease REM sleep during the first half-hour of recording without significantly altering the total REM sleep. The oral administration of cocaine produced effects that were qualitatively similar to those produced by the i.p. administration of this drug; although the magnitude of these effects was markedly reduced. During the first 4 h following injection of a 20-mg/kg (i.p.) dose of cocaine, REM sleep and SWS were significantly reduced from values obtained after the injection of vehicle.¹⁰ This dose of cocaine also significantly increased the time spent awake and latency for the onset of REM and SWS. The subsequent period between 4 to 8 h after the administration of a 20-mg/kg dose of cocaine did not significantly alter the sleep parameters from those seen in the vehicle condition. There are findings that suggest that low doses of cocaine may activate the reward systems associated with abuse liability of this drug. For example, the administration of cocaine in doses as low as 2.5 mg/kg (i.p.) have been shown to lower thresholds for rewarding brain stimulation.¹¹ Also, rats will self-administer cocaine intravenously in doses as low as 0.0375 mg/kg/infusion.¹² The above studies have shown relatively specific effects of cocaine on reward systems; however, no previous studies have examined the sleep–wake activity in the rat after the administration of low doses of cocaine. In the present study, polygraphic recordings were used to measure the wake–sleep patterns of freely moving rats after an injection (i.p.) of low doses of cocaine (ranging between 2.5 and 10 mg/kg).

Methods

Experimental subjects and housing

Experiments were performed on seven male Sprague–Dawley rats (Charles River, Wilmington, MA) weighing between 300 and 400 g. The rats were housed individually at 24°C with food and water provided ad libitum. Lights were on from 07.00 to 19.00 hours (light cycle) and off from 19.00 to 07.00 hours (dark cycle). The principles for the care and use of laboratory animals in research, as outlined by the National Institutes of Health Publication no. 85–23 (1985) were strictly followed.

Surgical procedures and implantation of electrodes

The treatment of the animals and surgical procedures were in accordance with an approved institutional animal welfare protocol. Efforts were made to minimize the number of animals and their suffering. The animals were anesthetized (pentobarbital, 40 mg/kg, i.p.), placed in a stereotaxic apparatus and secured using blunt rodent ear bars. A surgical plane of anesthesia was maintained with supplemental injections of chloral hydrate (60 mg/kg, i.p.) every 1–2 h, as necessary. The appropriate depth of anesthesia was judged by the absence of palpebral reflexes and by the absence of response to a tail pinch. The animals' core body temperature was maintained at $37^{\circ} \pm 1^{\circ}\text{C}$ with a thermostatic heating pad and a rectal feedback thermister probe. The scalp was cleaned and painted with providone iodine (Betadine). A scalp incision was made and the skin was retracted. The skull surface was cleaned in preparation for the implantation of electrodes. Potential postoperative pain was controlled with Torbugesic (Butorphanol Tartrate, 0.5 mg/kg, subcutaneous).

To record the behavioral states of vigilance, electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) electrodes were implanted as described in our earlier publications.^{13,14} To record cortical EEG, stainless steel screw (jewelers') electrodes, connected to Teflon-coated stainless steel wires, were screwed bilaterally into the skull (2.0 mm anterior and 3.5 mm lateral to the bregma). An additional electrode was screwed into the skull (4 mm anterior to bregma in the midline) to act as a reference electrode. To record hippocampal EEG (for hippocampal theta waves), Teflon-coated bipolar stainless steel macroelectrodes were placed stereotactically in the hippocampus (anterior: 4.8, lateral: 2.5 and horizontal: 4.0 and 3.0).¹⁵ A pair of Teflon-coated stainless steel wire electrodes were implanted bilaterally in the neck muscles for recording nuchal EMG. To record eye movements (EOG), two Teflon-coated silver wire electrodes were implanted in the external canthus muscle of one eye. All electrodes were secured to the skull with dental acrylic. Electrodes were crimped to miniconnector pins and brought together in a plastic connector. Immediately after surgery, the animals were placed in recovery cages and monitored for successful recovery from anesthesia and surgery. Successful recovery was gauged by the return of normal postures, voluntary movement and grooming. At this point the animals were transferred to their normal housing.

Habituation and polygraphic recordings

During recovery, habituation, and free moving recording periods, all rats were housed under a 12/12 h light/dark cycle (lights on from 07.00 to 19.00 hours.) with free access to food and water. Following a post-surgical recovery period of 3–7 days, the rats were habituated to a sound attenuated recording cage (size: 75 cm × 45 cm × 45 cm) and free-moving polygraphic recording conditions for 7–10 days. All adaptation-recording sessions were performed between 10.00. and 16.00 hours, when rats are normally sleeping.¹⁴

Injection protocol and experimental design

After adaptation-recording sessions, experimental recording sessions began. During each experimental recording session, at about 09.55 hours, the animals received a single injection (i.p.) of either the control vehicle (normal saline) or cocaine. Following the injection, the animals were connected to the polygraphic recording setup (Grass 79 polygraph and Rodent Sleep Stager software, Grass Instrument Division, Astro-Medical Inc., West Warwick, RI). Immediately after the completion of the injection and connection to the polygraphic recording plug, polygraphic variables were recorded continuously for a session of 6 h (between 10.00 and 16.00) when the rats would normally be sleeping. Each of these rats received a total of four injections (control saline, 2.5 mg/kg cocaine, 5.0 mg/kg cocaine and 10.0 mg/kg cocaine) in random order in four different experimental recording sessions. Each of these experimental sessions was separated by at least 3 days.

Determination of behavioral states and data analysis

For the purpose of determining possible effects on sleep and wakefulness, three behavioral states were distinguished based on the visual scoring of polygraphic data as described earlier.^{13,14} These three states were: (i) wakefulness (W): low voltage (50–80 μ V) fast (30–50 Hz) cortical EEG, high amplitude tonic and phasic EMG bursts, the presence of eye movements in the EOG and gross bodily movements; (ii) slow wave sleep (SWS): cortical EEG characterized by spindling and high voltage (200–400 μ V) slow waves (0.3–15 Hz), EMG tonus lower than during W and an absence of eye movements; and (iii) REM sleep: low voltage (50–100 μ V) and fast (20–40 Hz) cortical EEG, presence of muscle atonia, rapid eye movements and the presence of only theta waves (4–7 Hz) in the hippocampal EEG. All states were manually scored in 10-s epochs.

The polygraphic and behavioral measures provided the following dependent variables that are quantified for each trial: percentage of recording time spent in; (i) W; (ii) SWS; and (iii) REM sleep. The effects of the four different treatments (four treatments: three different doses of cocaine and saline control) on the percentages of W, SWS and REM sleep were statistically analyzed using one-factor ANOVAS (six ANOVAS for 6 1-h epochs following injections). Following one-factor ANOVAS, post hoc Scheffe *F*-tests were done to determine the individual levels of significant difference between the control (saline) and the three different doses of cocaine treatment at the six individual data points. Statistical analyses were performed with the use of StatView statistical software (Abacus Concepts, Berkeley, CA).

Results

Following all injections, while rats were in the recording cage and connected to the polygraphic recording setup, each animal's behavior was observed for approximately 1–2 h. Qualitatively, the control saline injection did not produce any obvious behavioral effect in the rats compared to behavior normally seen in similarly handled but uninjected rats. After each of the three doses of cocaine, the animals exhibited more exploratory behavior for about 30–45 min depending on the dose. After the higher dose, the animals spent a longer time in exploratory behavior, compared to after the lower dose. The rats bit inanimate objects inside the recording cage for about 1 h after the administration of the high dose of cocaine.

The changes in the percentage of time spent in wakefulness after the injection of the three different doses of cocaine are summarized in Figure 1. The total percentage of wakefulness in the first hour after the low dose of cocaine injection is significantly higher (Scheffe *F*-test, $F = 6.47$, $P < 0.01$) compared to the percentage after the injection of control saline (Fig. 1). The total percentages of wakefulness after the medium dose of cocaine injection were significantly higher than the control saline in the first ($F = 8.37$, $P < 0.001$) and second ($F = 3.61$, $P < 0.05$) hours of recordings. Similarly, after the high dose of cocaine injection the total percentages of wakefulness were significantly higher in the first ($F = 12.09$, $P < 0.001$), second ($F = 8.42$, $P < 0.001$), and third ($F = 4.52$, $P < 0.01$) hours of recordings (Fig. 1). These increased total percentages of wakefulness were mainly due to the longer duration of the waking episodes. These results indicate that the i.p. injection of cocaine increased the total time spent in wakefulness in a dose-dependent manner.

Shown in Figure 2 are the changes in the percentage of time spent in SWS after injection of the three different doses of cocaine. Statistical analysis (Scheffe *F*-tests) on the total percentage of time spent in SWS revealed that the percentage of SWS in the first hour of recording after the low dose of cocaine injection was significantly ($F = 5.44$, $P < 0.01$) less compared to the levels after control saline injection (Fig. 2). After the medium dose of cocaine injection, the total percentages of SWS were significantly less in the first ($F = 7.13$, $P < 0.01$) and second ($F = 3.70$, $P < 0.05$) hours of recordings compared to the percentage after control saline injection. Similarly, after the high dose of cocaine injection, the total percentages of time spent in SWS were significantly less in the first ($F = 10.16$, $P < 0.001$), second ($F = 8.72$, $P < 0.001$), and third ($F = 4.87$, $P < 0.01$) hours of recordings (Fig. 2). Decreased total percentages of SWS after the cocaine injection were due to both the increased latency and shorter durations of the SWS episodes. These findings indicate that the i.p. injection of cocaine in the freely moving rat dose-dependently reduced the time they spent in SWS.

The percentage of time spent in REM sleep after the injection of the control saline and three different doses of cocaine are presented in Figure 3. Individual comparisons (Post hoc Scheffe *F*-tests) showed that after the low dose of cocaine injection, the total percentages of REM were significantly higher in the second ($F = 3.25$, $P < 0.05$) and third ($F = 3.17$, $P < 0.05$) hours of recordings compared to those values after the control saline injection. This increased amount

of REM sleep after the low dose of cocaine was mainly due to the increased number of REM sleep episodes. The medium dose of cocaine injection suppressed REM sleep for the first 2 h and was followed by a slight, but still significant, increase in the total percentage of REM sleep in the fourth hour (Fig. 3). The high dose of cocaine injection eliminated REM sleep completely for the first 3 h. REM sleep began to appear in the fourth hour (Fig. 3). The decreased amount of REM sleep after medium and high doses of cocaine was due to increased latencies for the appearance of the first episode of REM sleep.

Discussion

The results of this study establish that a dose of cocaine as low as 2.5 mg/kg can produce significant alterations in sleep patterns in the rat. Their REM sleep was significantly higher in the second and third hours following the administration of a 2.5 mg/kg dose. The administration of the 5 mg/kg dose produced a suppression of REM sleep for 2 h followed by an increase over control values in total REM sleep in the fourth hour. The injection of the 10 mg/kg dose of cocaine, on the other hand, eliminated REM sleep for the first 3 h. In addition to these effects on REM sleep, cocaine administration also reduced SWS and increased the percentage of time of wakefulness in a dose-dependent manner. Reductions in REM sleep and SWS, as well as increases in the time spent awake, have been previously shown to occur in the rat following the administration of either cocaine^{9,10} or other psychomotor stimulants such as D-amphetamine.¹⁶ The significant increase in REM sleep produced by the administration of low doses of cocaine in this study has not been previously reported, although a trend in this direction was detected in an earlier study.⁹ Cocaine was administered in the present study on what can be characterized as a subacute acute basis. Similar schedules of administration are used frequently in studies of the rewarding effects of cocaine.¹¹

The administration of psychomotor stimulants other than cocaine, including amphetamine and methamphetamine, to rats may result in a rebound in both REM sleep and SWS several hours later during the day in which these drugs were administered.^{17,18} REM sleep, however, may not increase above control levels.¹⁹ After initially producing decreased SWS and REM sleep resulting in increased wakefulness, the chronic administration of high doses of cocaine to rats is followed by a rebound increase in REM sleep and SWS observed 12 h later, during the daily dark phase.¹⁰ In human cocaine users, rebound increases in REM sleep have been observed during periods of withdrawal from this drug,^{6,8} although this has not been a consistent finding.⁵ It is not yet clear whether the increases in REM sleep produced by low dose cocaine administration is mechanistically related to the rebound REM sleep that results from either amphetamine administration or chronic cocaine use. It should be noted, that in contrast to the effects of amphetamine, treatment with low dose cocaine resulted in increases in REM sleep that did not occur in association with concurrent changes in other sleep parameters.

After an intraperitoneal injection, cocaine serum levels peak very rapidly.²⁰ The serum half-life of cocaine has been determined to be approximately 13 min. Thus, at the times at which REM sleep was found to increase following administration of low dose cocaine in the present study, blood concentrations of this drug would have dropped markedly from their initial levels. The possibility then exists that increases in REM sleep seen subsequent to cocaine administration are produced by some later response to cocaine exposure rather than to the direct actions of this stimulant, or they may reflect the actions of very low concentrations of this drug. However, we acknowledge that these possible explanations would have to be supported by future experiments.

Cocaine selectively blocks monoamine transporter proteins. *In vitro*, the IC₅₀s for the cocaine-induced blockade of dopamine, serotonin and norepinephrine transporters are all within the same order of magnitude as each other.^{21,22} Amphetamine-induced arousal and waking may

be mediated, in part, by the actions of norepinephrine.^{19,23} Some findings suggest that dopamine also may play a role in mediating the effects of psychomotor stimulants on wakefulness. The relative potencies of D-, L-, and methamphetamines in producing wakefulness in the dog correlate with their effects on dopamine efflux in the caudate nucleus.²⁴ Furthermore, dopamine transporter knockout mice are unresponsive to the wakefulness-promoting effects of either methamphetamine or the selective dopamine reuptake blocking agent GBR 12909.²⁵ It is not yet clear whether wakefulness is increased during psychomotor stimulant administration by the actions of dopamine on the neural mechanisms that regulate natural sleep or by a secondary processes that increases locomotor activity.

Serotonin released from the dorsal raphe nucleus and norepinephrine from the locus coeruleus can suppress the activity of brain stem neurons that are involved in the generation of REM sleep.^{26,27} Thus, the reductions in REM sleep that were produced by the administration of moderate doses of cocaine in the present study may have due to the inhibition of serotonin and/or norepinephrine reuptake by this drug.

What role, if any, elevations in brain monoamine levels produced by low doses of cocaine play in the increase in REM sleep exhibited after administration remains to be established. The acute administration of cocaine may produce feedback inhibition of serotonin and norepinephrine synthesis and turnover.^{28–31} Cocaine-induced inhibition of serotonin or norepinephrine synthesis could then be associated with the elevations in REM sleep observed after the administration of low dose cocaine. In one study, recovery from cocaine-induced suppression of serotonin synthesis was found to occur between 120 and 150 min after the administration of this drug in doses ranging between 3.0 and 18.2 mg/kg i.p.³⁰ In the present study, however, cocaine induced-elevations in REM sleep produced by the 2.5 and 5 mg/kg doses of cocaine were found to persist for more than 3 h. Thus, the elevation of REM sleep seen following the administration of low dose cocaine appears to continue for several hours after the inhibition of serotonin synthesis by this agent has subsided.

In the present study, cocaine was found to have two different effects on REM sleep and/or wakefulness, depending on the dose administered. In two other studies, a similar pattern of responses was seen when glutamate was microinjected into the pedunculopontine tegmentum (PPT).^{32,33} Glutamate promoted REM sleep at low concentrations and wakefulness at higher concentrations. The similarity of the effects between glutamate and cocaine suggest that the possibility that the disparate alterations in sleep patterns observed post-administration of different doses of cocaine might involve a glutamatergic mechanism. This may involve the indirect actions of cocaine on pathways that influence the PPT.

In addition to its direct effects in the brainstem, cocaine could influence REM sleep through the extensive connections that exist between the PPT and the other brain regions that mediate the actions of this drug. These connections include cholinergic projections from the PPT to regions that are densely populated with dopaminergic neurons; notably the substantia nigra³⁴ and the ventral tegmental area.³⁵ In addition, afferents to the PPT originating from basal ganglia structures including the substantia nigra³⁶ and several limbic structures, such as the bed nucleus of the stria terminalis and the central nucleus of the amygdala, may also have a role.³⁷

Consistent with the results of previous studies, it has been shown here that the subacute administration of cocaine results in an increase in wakefulness and decrease in SWS. These effects occur in a dose-dependent manner. While the higher doses of cocaine used in this study were found to initially reduce REM sleep, this stage of sleep increased above control levels a few hours following the administration of lower doses of cocaine. The neuronal mechanism that produces this latter effect remains to be elucidated. The PPT, which plays a critical role

in the generation of REM sleep, has been suggested to play a role in the reinforcing effects of cocaine, nicotine,^{38,39} amphetamine^{40,41} and morphine.^{40,42} Determination of the extent to which there is a functional overlap in the neuronal populations that regulate REM sleep and drug-induced reinforcement in the PPT might greatly help in understanding the processes that are associated with the development of drug dependence.

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Figure 1.

Effects of different doses of cocaine on percentages of wakefulness. Bar represents percentages (means and SD) of wakefulness every hour for a 6-h period of time after intraperitoneal injection of control vehicle (normal saline) and three different doses of cocaine. Note the significant dose-dependent increase of wakefulness after the cocaine injection. Note also that the low dose of cocaine-induced increase in wakefulness is significant only for 1 h. (□) control saline; (▤) 2.5 mg/kg cocaine, (■) 5.0 mg/kg cocaine; (▥) 10mg/kg cocaine. These *P*-values represent the comparison with control saline. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

Figure 2.

Effects of different doses of cocaine on percentages of slow-wave sleep (SWS). Bar represents percentages (means and SD) of SWS every hour for a 6-h period of time after an intraperitoneal injection of the control vehicle (normal saline) and three different doses of cocaine. Note a significant dose-dependent reduction of slow-wave sleep after the cocaine administration. (□) control saline; (■) 2.5 mg/kg cocaine, (■) 5.0 mg/kg cocaine; (■) 10mg/kg cocaine. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. These P -values represent the comparison with control saline.

Figure 3.

Effects of different doses of cocaine on percentages of REM sleep. Bar represents percentages (means and SD) of REM sleep every hour for a 6-h period of time after intraperitoneal injection of control vehicle (normal saline) and three different doses of cocaine. Note a significant increase in REM sleep in the second, third, and fourth hours after the 2.5 mg/kg dose of cocaine injections. After the 5 mg/kg dose of cocaine injections total percentage of REM sleep was significantly less in the second hour due to the delayed onset of REM sleep, however, in the third, fourth and fifth hours the total percentage of REM sleep was significantly higher than the control. After the high dose (10 mg/kg) of cocaine, REM sleep was suppressed for four hours without an increase in the final two hours. (□) control saline; (■) 2.5 mg/kg cocaine, (■) 5.0 mg/kg cocaine; (■) 10mg/kg cocaine. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. These P -values represent the comparison with control saline.