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Lesions of the dorsomedial frontal cortex block sensitization to the positive-reinforcing effects of cocaine

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Abstract

Previous studies have reported that rats exposed to a binge-abstinence history of cocaine self-administration exhibit sensitization to the positive-reinforcing effects of cocaine on a progressive ratio (PR) schedule of reinforcement. The purpose of the present study was to determine whether lesions of the dorsomedial frontal cortex block sensitization to the reinforcing effects of cocaine in rats with a history of binge-abstinence self-administration. Separate groups of male rats received bilateral infusions of either ibotenic acid (lesion) or sterile saline (sham) into the dorsomedial frontal cortex, or were left undisturbed (intact). All rats were then implanted with jugular catheters and trained to self-administer cocaine. Following acquisition, cocaine was made available on a PR schedule of reinforcement and breakpoints were determined in each group. Rats were then exposed to a discrete-trials (DT) procedure in which cocaine was made available during 10-min discrete-trials that occurred every 15 min (i.e., 4 times per hr) during daily, 24-hr sessions. This procedure elicited a "binge" in all groups, during which high rates of responding were maintained over a period of 1–2 days. After 10 days, the DT procedure was terminated, and no cocaine was available for the next 7 days. Following 7 days of forced "abstinence", cocaine-reinforced breakpoints were redetermined on the PR schedule. Prior to the DT procedure, no differences were observed in breakpoints across the three groups. Following the 7-day abstinence period, breakpoints on the PR schedule increased significantly in intact and sham rats, indicating an increase in the reinforcing efficacy of cocaine. In contrast, breakpoints did not increase in lesion rats, and were similar to those obtained prior to the binge-abstinence history. These data suggest that lesions of the dorsomedial frontal cortex block sensitization to the positive-reinforcing effects of cocaine in rats with a history of binge-abstinence self-administration.

Keywords: Cocaine; Ibotenic acid; Lesion; Frontal cortex; Positive reinforcement; Rat; Self-administration; Sensitization

Sensitization refers to an increase in sensitivity to the effects of a drug following its repeated administration (Feldman et al., 1997). Sensitization can be observed with a number of drugs, but is particularly robust following the repeated, intermittent administration of psychomotor stimulants. The repeated administration of cocaine, for instance, results in a progressive increase in its ability to stimulate locomotor activity and produce stereotypy in experimental animals (Schuster and Bates, 1977; Post et al., 1988; Sorg and Steketee, 1992; Shumsky et al., 1997; Shultz et al., 1999; Sabeti et al., 2003). Pre-exposure to cocaine also facilitates the acquisition of drug-seeking behavior in self-administration studies (Schenk and Partridge, 2000; Childs et al., 2006), and increases breakpoints maintained by cocaine on a progressive ratio (PR) schedule of reinforcement (Covington and Miczek, 2001). These findings have led some investigators to propose that sensitization to the positive-reinforcing effects of cocaine and other drugs of abuse is a contributing factor in the transition from casual drug use to compulsive drug use that is characteristic of human substance-abusing populations (Wise and Bozarth, 1987; Kalivas et al., 1998; Robinson and Berridge, 2000, 2001).

The neural mechanisms mediating the acute effects of cocaine and other psychomotor stimulants are well understood. These drugs increase synaptic concentrations of monoamines through their interaction with monoamine transporters (Rothman and Baumann, 2003; Riddle et al., 2005). Their effects on

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locomotor activity and their ability to function as positive reinforcers are attributable to their ability to increase dopamine transmission in mesolimbic and mesocortical pathways that originate in the ventral tegmental area and terminate in the nucleus accumbens and frontal cortex (Kelly and Iversen, 1976; Roberts and Koob, 1982; Goeders and Smith, 1983; Delfs et al., 1990). There is also an increasing body of knowledge regarding the mechanisms by which these drugs produce sensitization. For instance, studies have shown that the initiation of sensitization is due to a series of rapidly developing but relatively transient neural adaptations in the ventral tegmental area (Henry et al., 1989; Ackerman and White, 1990), and that the maintenance and expression of sensitization is due to a succession of slowly developing but long-lasting adaptations in the nucleus accumbens (Henry and White, 1991, 1995).

In addition to these mechanisms, several converging lines of evidence suggest that excitatory amino acid projections from the frontal cortex also play a critical role in the development and expression of sensitization. For example, repeated cocaine administration produced long-term enhancement of cortical-striatal signaling from frontal cortex (Canales et al., 2002). In addition, electrical kindling of the frontal cortex produces sensitization to the effects of cocaine on locomotor activity that is indistinguishable from that produced by repeated drug administration (Schenk and Snow, 1994). Furthermore, sensitization to the locomotor effects of cocaine is blocked by systemic administration of the NMDA-receptor antagonist MK-801 (Karler et al., 1989, 1994; Wolf and Jeziorski, 1993; Li et al., 1999) and the AMPA-receptor antagonists DNQX (Karler et al., 1994) and NBQX (Li et al., 1997, 1999), presumably by preventing the neuronal adaptations that are responsible for the induction and expression of sensitization (Masserano et al., 1996; Li et al., 1999). Finally, lesions of the frontal cortex, particularly those targeting the dorsal regions of the prefrontal cortex, block the development (Tzschentke and Schmidt, 1998; Li et al., 1999) and expression (Pierce et al., 1998) of sensitization to cocaine's effects on locomotor activity.

Although studies involving non-contingent drug administration have been critical in increasing our understanding of the neuronal mechanisms contributing to sensitization, they do not mimic the specific drug-seeking and drug-taking behaviors that are believed to mediate the transition from casual drug use to compulsive drug use in human drug addicts. We recently developed an animal model of drug self-administration that mimics the binge-abstinence pattern of drug use commonly reported in human cocaine abusers (Gawin, 1991; Pottieger et al., 1995). In our model, cocaine is self-administered in a discrete-trials (DT) procedure that permits 24-hr access to cocaine without producing signs of toxicity that is often characteristic of extended-access conditions (Bozarth and Wise, 1985). Rats exposed to this procedure exhibit an initial "binge" lasting 24–36 hr, followed by a circadian pattern of drug intake for the remainder of the procedure. This is followed by a 7-day period of forced abstinence, after which the reinforcing effects of cocaine are examined on a PR schedule of reinforcement. In a series of studies, we reported that this history of binge-abstinence self-administration produces a robust and long-lasting sensitization to the positive-reinforcing effects of cocaine, as revealed by increases in breakpoints maintained by cocaine on the PR schedule (Morgan et al., 2002, 2005; Morgan and Roberts, 2004).

In the present study, we examined the ability of lesions of the dorsomedial frontal cortex to block sensitization to the positive-reinforcing effects of cocaine in rats with a history of binge-abstinence self-administration. Separate groups of rats received either bilateral ibotenic acid lesions of the dorsomedial frontal cortex, bilateral sham lesions of the dorsomedial frontal cortex, or were left intact. All groups were then surgically implanted with indwelling venous catheters and trained to self-administer cocaine under positive-reinforcement contingencies. Once self-administration was established, the reinforcing effects of cocaine were examined on a PR schedule of reinforcement. This was followed by a 10-day period of cocaine exposure in a DT procedure, a subsequent 7-day period of forced abstinence, and then a redetermination of cocaine's effects on the PR schedule. We hypothesized that ibotenic acid lesions of the dorsomedial frontal cortex would block sensitization to the positive-reinforcing effects of cocaine.

1. Materials and methods

1.1. Animals

Subjects were male, experimentally naïve, Sprague-Dawley rats (Harlan, Indianapolis, IN, USA) weighing approximately 350g at the start of the experiment. Rats were housed individually in a large colony room on a reverse light/dark cycle (lights on: 15:00), with food and drinking water freely available in the home cage. All subjects were maintained in accordance with the guidelines of the Institutional Animal Care and Use Committee of Wake Forest University and the *Guide for the Care and Use of Laboratory Animals* (Institute of laboratory Animals Resources, 1996). After a minimum 3-day acclimation period, individual rats were randomly assigned to lesion, sham, or intact conditions.

1.2. Surgical procedures

Rats assigned to the lesion and sham groups were anesthetized with a combination of ketamine HCl (100 mg/kg i.p.) and xylazine (8.0 mg/kg i.p.) and placed in a stereotaxic apparatus (Kopf Instruments, Tujunga, CA, USA). The scalp was retracted and bilateral holes were drilled in the skull above the infusion sites. The needle from a 10 µl syringe (Hamilton Company, Reno, NV, USA) was then lowered to the following coordinates relative to bregma (Paxinos and Watson, 1998): AP+2.7 mm, ML±0.7 mm, DV-2.5 mm. In lesion rats, 0.5 µg/0.5 µl ibotenic acid was slowly infused over a period of approximately 2 min. The needle was left in place for an additional 5 min to permit the solution to diffuse away from the infusion site. The needle was then inserted into the opposite hemisphere and the procedure was repeated. In sham rats, sterile saline was infused in lieu of ibotenic acid. Once the needle was retracted, the incision was closed and butorphanol HCl (1.0 mg/kg, s.c.) was

administered as a post-surgical analgesic. All subjects were allowed 7 days to recover before catheter implantation. Intact rats were left undisturbed.

All rats were implanted with chronic indwelling catheters (CamCaths, Cambridge, UK) under ketamine and xylazine anesthesia. Catheters were placed in the right jugular vein and exited the skin on the dorsal surface of the scapulae according to procedures described previously (Roberts and Goeders, 1989). After awakening from anesthesia, rats were placed in individual 30×30×30 cm operant conditioning chambers that served as the animals' home cages for the remainder of the study. Each catheter was connected through a stainless-steel protective spring to a counter-balanced swivel that allowed the rat to move freely within the chamber.

1.3. Behavioral training and determination of initial breakpoints

At the start of behavioral training, a retractable lever was extended into the chamber and lever pressing was reinforced on a fixed ratio 1 (FR1) schedule of reinforcement. On this schedule, each lever press activated an infusion pump that administered 1.5 mg/kg/infusion cocaine over a 4–5 s duration (based on body weight). Concurrent with the start of each infusion, the lever was retracted, and a stimulus light located above the lever was illuminated to signal a 20-s post-infusion time-out. During the initial training sessions, rats could obtain a maximum of 40 infusions during each 24-hr session. Once 40 infusions were delivered, the lever was retracted and no further infusions were available until the beginning of the next session. When rats exhibited a stable pattern of responding on the FR1 schedule over 5 consecutive days (defined as 40 infusions within 6 hr and with regular post-infusion pauses), reinforcement contingencies were changed such that responding was maintained on a PR schedule of reinforcement.

On the PR schedule, the number of responses required for a cocaine infusion incremented through the following progression: 1, 2, 4, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 323, 402, 492 and 603 (see Richardson and Roberts, 1996, for complete algorithm). Each session continued until a breakpoint was reached, with breakpoint defined as the number of infusions obtained before one hour elapsed with no infusions. Daily PR sessions continued until breakpoints were stable (i.e., 3 consecutive days in which the breakpoint varied by no more than 3 increments with no increasing or decreasing trends). Once this criterion was met, the DT procedure was introduced.

1.4. Binge-abstinence self-administration

In the DT procedure, subjects were given access to cocaine during four discrete-trials each hr, throughout daily, 24-hr sessions. In these sessions, a trial began every 15 min with the introduction of the retractable lever into the chamber. A single lever press during the trial resulted in a cocaine infusion, retraction of the lever, and illumination of the stimulus light for 20s to signal the termination of the trial. The trial was terminated automatically if 10 min elapsed without a lever press. Discrete-trials occurred at 15 min intervals, 24 hr per day, for 10 consecutive days.

Following the last trial of the DT procedure, all rats began a 7-day period of forced abstinence. During this period, the lever was retracted, the stimulus light was turned off, and no cocaine was delivered. Catheters were flushed daily with heparinized saline to maintain patency.

1.5. Redetermination of breakpoints

After 7 days of abstinence, a single FR session was conducted to test for catheter patency. If the subject received 40 infusions within a 6-hr period with regular post-infusion pauses, then schedule contingencies were changed on the following day, and responding was reinforced on a PR schedule of reinforcement. Daily PR sessions continued until breakpoints were stable (see above). If catheter patency was lost at any point prior to the final determination of breakpoint, then the rat was removed from the study. A loss of catheter patency resulted in the removal of 4, 2 and 3 rats from the intact, sham and lesion groups, respectively.

1.6. Data analysis

The primary dependent measure was breakpoint (defined as number of infusions) on the PR schedule of reinforcement. These data were analyzed via repeated-measures ANOVA, with group (intact vs. sham vs. lesion) serving as a between-subjects factor and history (baseline determination vs. final determination) serving as the repeated measure. As a secondary analysis, difference scores for each group were obtained by subtracting the number of infusions obtained under baseline conditions from the number of infusions obtained after the binge-abstinence history. These data were analyzed via one-way ANOVA using group as a factor. All data from the DT procedure were examined via repeated-measures ANOVA, with group serving as a between-subjects factor and day (1–10) serving as the repeated measure. Data on acquisition and from the FR schedule were analyzed via one-way ANOVA using group as a factor. For all statistical tests, the alpha level was set at $p < 0.05$.

1.7. Histology

Following redetermination of final breakpoint, lesion rats were prepared for histological examination (see below). Visual examination suggested the presence of lesions in all animals; however, the precise boundaries of the lesion could not be confidently assessed because the brain surface had collapsed inward at the lesion site by this point (40 to 50 days after surgery). An additional group of 5 rats was therefore prepared that were used exclusively for histological purposes. These rats received bilateral ibotenic acid lesions of the dorsomedial frontal cortex according to the procedures described above. After 7 days, the rats were deeply anesthetized and perfused transcardially with 100 ml 0.9% saline followed by 100 ml fixative (4% paraformaldehyde, 14% v/v saturated picric acid,

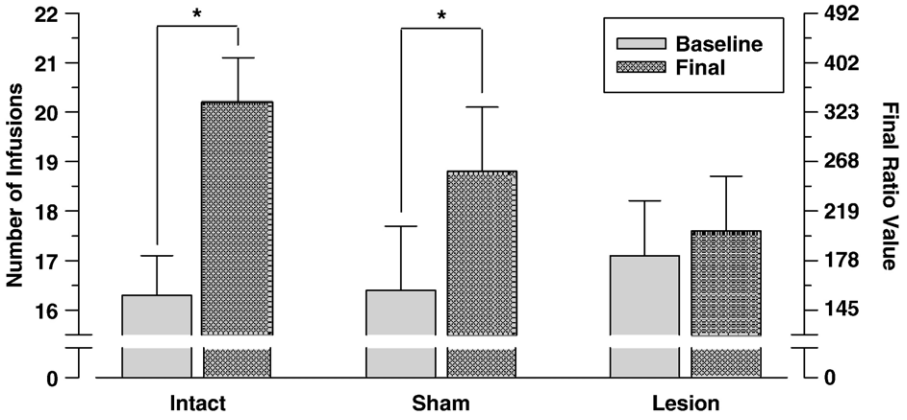

Fig. 1. Breakpoints on a PR schedule before (baseline) and after (final) a history of binge-abstinence cocaine self-administration. Left axis depicts the number of infusions obtained; right axis depicts the final ratio value completed. Vertical lines represent the SEM. Data are shown from intact, sham and lesion rats.

125 mM sodium phosphate). The brains were subsequently removed and kept in fixative for 90 min before being stored in 10% sucrose. Brains were sliced in a −19° cryostat in 20 μm slices and mounted onto slides for thionin staining. Histopathological evaluation of the brain lesions were then conducted for each subject using light microscopy.

2. Results

2.1. Acquisition and determination of initial breakpoints

A total of 7 intact rats, 6 sham rats, and 10 lesion rats completed all phases of the study. Rats from the intact, sham and lesion groups acquired cocaine self-administration in a mean (SEM) of 4.4 (0.8), 4.5 (0.5) and 4.7 (1.1) days, respectively. On the FR schedule, rats received the maximum number of 40 reinforcers in a mean (SEM) of 298 (17), 331 (22), and 325 (22) min, respectively. Initial breakpoints on the PR schedule were similar across groups, ranging from 16.2 to 17.1 (Fig. 1). One-way ANOVAs using group as a factor did not reveal any significant differences on days to acquisition, rate of responding on the FR schedule, or initial breakpoints on the PR schedule (p's > 0.05).

2.2. DT procedure responding

Responding in the DT procedure was characterized by an initial "binge", during which almost every available infusion was obtained for the first 24–36 hr (Fig. 2). After the first day, the number of infusions decreased, and a circadian pattern of responding was seen in all animals (Fig. 3). Both the initial binge and the subsequent circadian pattern of responding were evident in all groups, and very few differences were observed across individual rats. A repeated-measures ANOVA revealed a significant main effect of day, F (9, 180) = 25.393, p < 0.001, but no effect of group or group×day interaction. Post-hoc tests revealed that a significantly greater number of infusions were obtained on the first day (i.e., during the initial binge) than on every subsequent day of the schedule (p's < 0.001).

2.3. Redetermination of breakpoints

Following the binge-abstinence history of self-administration, breakpoints on the PR schedule were redetermined. Relative to the original determination, breakpoints increased in intact and sham rats, but not in lesion rats (Fig. 1). A repeated-measures ANOVA revealed a significant main effect of history, F (1, 20) = 17.139, p = 0.001 and a significant group×history interaction, F (2, 20) = 13.123, p = 0.035. Post-hoc tests indicated that increases in breakpoints were statistically significant in intact (p = 0.015) and sham (p = 0.019) rats, but not in lesion rats. In regard to magnitude, these increases were greatest in intact rats, intermediate in sham rats, and smallest in lesion rats (Fig. 4). A one-way ANOVA comparing these differences revealed a significant main effect of group, F (2, 22) = 3.855, p = 0.038, and post-hoc tests revealed that the difference between intact rats and lesion rats was statistically significant (p = 0.023). These effects were also apparent in data from individual rats,

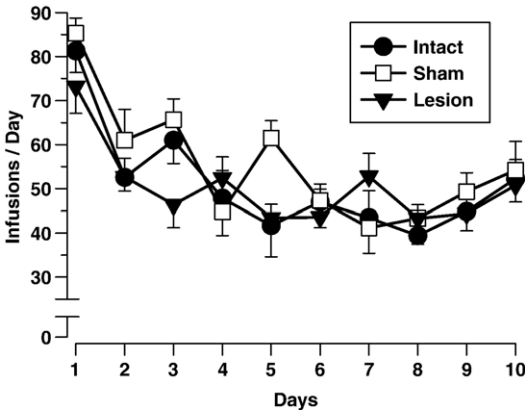

Fig. 2. Mean number of infusions per day in the DT procedure. In this procedure, cocaine was made available during 10-min discrete-trials that occurred every 15 min (i.e., 4 times per hr) during daily, 24-hr sessions. Completion of one lever press resulted in an infusion of cocaine and termination of the trial. Vertical lines represent the SEM; where not indicated, the SEM fell within the data point. Data are shown from intact, sham and lesion rats.

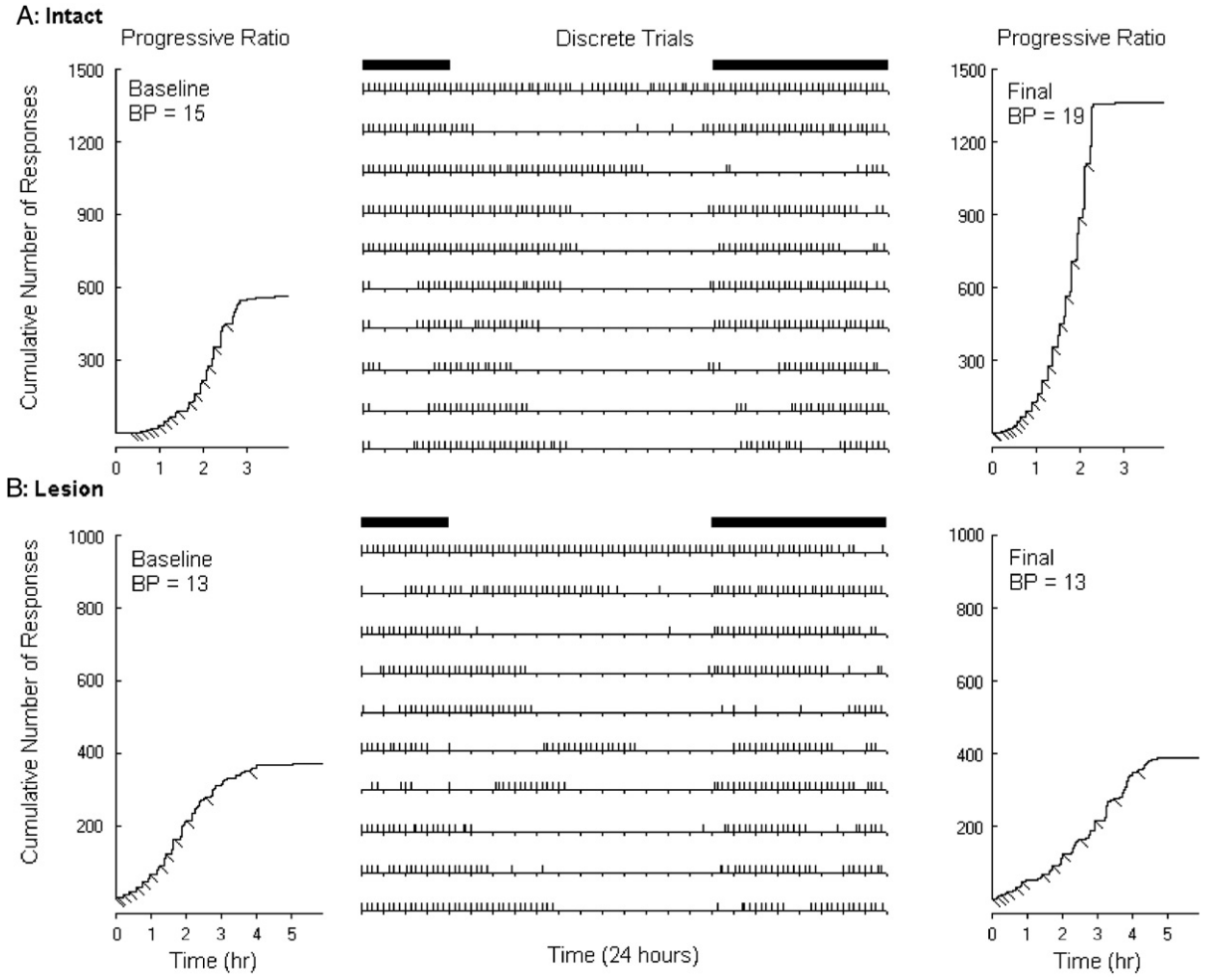

Fig. 3. Cumulative and event records from representative intact (A) and lesion (B) rats. Left panels depict cumulative number of responses on the PR schedule under baseline conditions. Downward deflections reflect cocaine infusions. The breakpoint (BP) was defined as the number of infusions obtained before responding ceased for one hour. Center panels depict responding maintained by cocaine in the DT procedure across 10 days. Vertical dashes reflect lever presses/cocaine infusions. Dark horizontal bar indicates the dark phase of the 24-hr cycle. Right panels depict cumulative number of responses on the PR schedule following a history of binge-abstinence self-administration. Note: Baseline breakpoints and responding maintained by cocaine in the DT procedure did not differ between the two rats; however, breakpoints following a history of binge-abstinence self-administration increased in the intact rat but not the lesion rat.

even under conditions in which baseline breakpoints and responding on the DT schedule did not differ (Fig. 3).

2.4. Histology

Histological examination of rats receiving ibotenic acid lesions 7 days prior to sacrifice revealed small and discrete lesions confined to the dorsomedial frontal cortex (Fig. 5). All five rats exhibited damage to the premotor cortex, with lesser damage to the anterior cingulate and dorsal regions of the prelimbic cortex. None of the rats exhibited damage to the ventral regions of the prefrontal cortex, including the infralimbic cortex. The maximal extent of cell loss and gliosis ranged from +2.2 to+4.7 mm relative to bregma (Paxinos and Watson, 1998), and lesions were generally similar between the two hemispheres.

3. Discussion

In the present study, a history of binge-abstinence self-administration produced sensitization to the positive-reinforcing effects of cocaine in intact and sham-lesioned animals. As measured by the number of reinforcers (i.e., infusions) obtained within a session, breakpoints increased in intact rats from 16.2 at baseline to 20.2 at the final determination. When these values are considered in terms of total number of responses, intact rats emitted approximately 1000 more responses over the course of a session at endpoint relative to baseline. These effects could be observed clearly in individual animals, with the majority of rats continuing to respond at rapid and consistent rates for longer periods of time before reaching a breakpoint. As reported previously (Morgan et al., 2002, 2005; Morgan and Roberts, 2004), the binge-abstinence model appears to be a reliable method of producing sensitization to the positive-reinforcing effects of cocaine that mimics, in many respects, the patterns of drug self-administration commonly observed in human drug addicts.

In contrast to that seen in intact and sham-lesioned animals, sensitization was not observed in rats with ibotenic acid lesions of the dorsomedial frontal cortex. In these animals, breakpoints at endpoint were similar to, and not significantly different from,

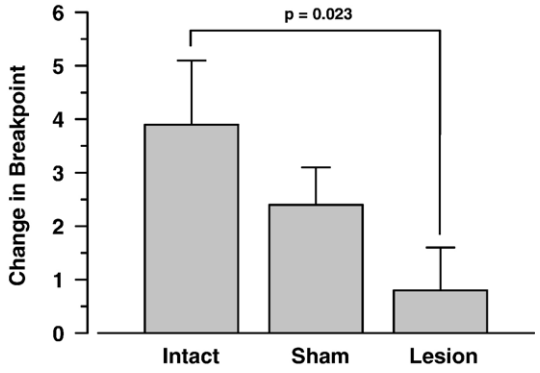

Fig. 4. Change in cocaine-maintained breakpoints (i.e., number of infusions obtained) on a PR schedule of reinforcement. Data were obtained by subtracting the number of infusions obtained under baseline conditions from the number of infusions obtained following a history of binge-abstinence self-administration. Vertical lines represent the SEM. Data are shown from intact, sham and lesion rats.

breakpoints obtained at baseline. Analysis of within-session responding from individual rats revealed that the rate and duration of responding was indistinguishable between the two determinations, resulting in similar breakpoints and total number of responses per session. To our knowledge, this is the first demonstration that lesions of the dorsomedial frontal cortex block sensitization to the positive-reinforcing effects of cocaine. These findings support and extend those from several previous studies showing that lesions of the dorsomedial frontal cortex block sensitization to the effects of cocaine on more general indices of behavior, such as locomotor activity and rearing (Pierce et al., 1998; Tzschentke and Schmidt, 1998; Li et al., 1999).

Although large differences were seen between groups at endpoint, no between-group differences were observed on cocaine self-administration prior to the binge-abstinence history. The three groups were similar in regard to the number of days necessary to acquire cocaine self-administration and rate of responding on the FR schedule of reinforcement. It is also important to note that cocaine-maintained breakpoints did not differ between the three groups prior to the binge-abstinence history, suggesting that dorsomedial frontal cortex lesions do not alter the positive-incentive properties of cocaine in the absence of sensitization. This finding is consistent with an early study reporting that 6-hydroxydopamine (6-OHDA) lesions of the prefrontal cortex do not influence cocaine self-administration on an FR1 schedule of reinforcement (Martin-Iverson et al., 1986); however, it should be noted that other studies have reported that both 6-OHDA (Schenk et al., 1991; McGregor et al., 1996) and quinolinic acid (Weissenborn et al., 1997) lesions of the prefrontal cortex increase cocaine self-administration under some conditions. Responding in the DT procedure was also similar between the three groups. In all rats, responding in this procedure was characterized by an initial binge lasting 24 to 36 hr, followed by a circadian pattern of responding for the remainder of the procedure. Analysis of individual data revealed that neither the number of responses nor the temporal distribution of responses during daily DT sessions differed across the three groups. Importantly, this finding rules out the possibility that different amounts or patterns of drug intake could account for the asymmetrical development of sensitization following the binge-abstinence history.

In the present study, all experimental lesions were induced prior to cocaine exposure, so it is not known whether the lesions blocked the development of sensitization, the expression of sensitization, or a combination of both. Previous studies examining sensitization to cocaine's locomotor effects have tended to follow a similar protocol, inducing experimental lesions prior to drug exposure. For instance, Li et al. (1999) and Tzschentke and Schmidt (1998) reported that lesions of the dorsal prefrontal cortex blocked the development of sensitization when induced 7 days and 10 days prior to cocaine exposure, respectively. In contrast, Pierce et al. (1998) induced experimental lesions during a three-week withdrawal period following repeated daily injections of cocaine. In that study, lesions of the dorsal prefrontal cortex blocked completely the expression of sensitization. It is possible that the frontal lesions induced in the present study exerted a similar, and possibly selective, influence on the expression of cocaine sensitization; however, this possibility will have to be addressed in future studies.

Histological examination of rats receiving ibotenic acid lesions 7 days prior to sacrifice revealed that all lesions were uniformly small and confined to the dorsomedial frontal cortex. This region comprises the premotor cortex and the dorsal prefrontal cortex. The dorsal prefrontal cortex includes the anterior cingulate and the prelimbic cortex, an area that sends excitatory amino acid afferents to the ventral tegmental area and the nucleus accumbens core (Phillipson and Griffiths, 1985; Berendse et al., 1992; Wright and Groenewegen, 1995). None of the lesions extended to ventral prefrontal cortex, which includes the infralimbic cortex and sends afferent projections to the nucleus accumbens shell (Brog et al., 1993; Kalivas, 1993; Wright and Groenewegen, 1995). In contrast to the dorsal prefrontal cortex, the ventral prefrontal cortex does not appear to play a role in cocaine sensitization, as lesions of the ventral prefrontal cortex do not block sensitization to the locomotor

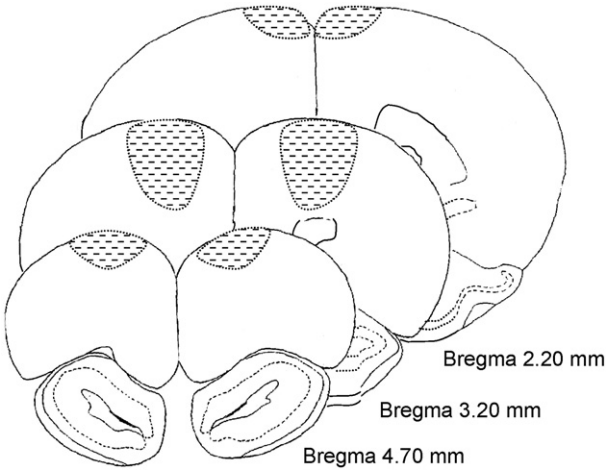

Fig. 5. Location and extent of ibotenic acid lesions of the dorsomedial frontal cortex. Shaded areas represent maximal extent of cell loss and gliosis in 5 rats receiving lesions 7 days prior to sacrifice. Lesions were generally similar between the two hemispheres.

effects of cocaine (Pierce et al., 1998; Tzschentke and Schmidt, 1998, 2000).

In all rats examined, the most severe damage was seen in the frontal cortical area labeled "premotor cortex" (Paxinos and Watson, 1998), an area that sends excitatory amino acid projections to the dorsal striatum to mediate the selection and planning of voluntary motor movement (Hoshi and Tanji, 2004). Although not typically considered part of the reward pathway, the premotor cortex uses information about expected rewards to mediate goal-directed behaviors that lead to positive reinforcement (Elliott et al., 2003). Acute administration of psychomotor stimulants increases extracellular dopamine concentrations in the premotor cortex (Moghaddam et al., 1993), and repeated administration of cocaine upregulates dopamine D2 receptors (Macêdo et al., 2001) and alters the morphology of pyramidal motor neurons (Ballesteros-Yanez et al., 2007) in this area. Importantly, repeated cocaine administration produces long-term enhancement of cortical-striatal signaling from premotor and motor cortices (Canales et al., 2002), which may contribute to the development of sensitization. Although it is difficult to isolate the relative influence of the premotor cortex in the present findings, the extensive damage to this area observed in the lesion animals suggest that further research into its role in sensitization and cocaine reinforcement is warranted.

A large body of clinical evidence now indicates that the dorsomedial frontal cortex plays an important role in a variety of addiction-related processes in human drug-abusing populations. For instance, neuroimaging studies have reported increased blood flow in the prefrontal cortex during craving induced by cocaine and cocaine-related cues (e.g., Grant et al., 1996; Breiter et al., 1997; Maas et al., 1998; Wang et al., 1999; Wexler et al., 2001), and a recent study reported that relapse to cocaine abuse is associated with metabolic activation of the premotor cortex during cue-induced craving (Kosten et al., 2006). Such findings have led some researchers to suggest that hyperactivity of the frontal cortex could trigger compulsive drug intake, in much the same way this area have been implicated in the compulsive behaviors seen in individuals with obsessive-compulsive disorder (Volkow et al., 2004). If this hypothesis is accurate, drugs that target the excitatory amino acid afferents from the frontal cortex may hold potential for treating the compulsive drug-seeking behaviors that characterize cocaine abuse and dependence. Consistent with this possibility, antagonists of NMDA (Allen et al., 2005; Pulvirenti et al., 1997; Hyytia et al., 1999; Shoaib et al., 1995; but see Ranaldi et al., 1996; Pierce et al., 1997), AMPA (Backstrom and Hyytia, 2003, 2006) and metabotropic glutamate receptors (Peters and Kalivas, 2006; Adewale et al., 2006; Paterson and Markou, 2005; Lee et al., 2005) have shown promise in animal models of drug-seeking behavior. Also consistent with this possibility, selective agonists at group II metabotropic glutamate receptors, which act to reduce evoked glutamate release, reduce cue-induced reinstatement of cocaine (Baptista et al., 2004) and heroin (Bossert et al., 2004, 2006) self-administration.

In the present study, a history of binge-abstinence self-administration produced sensitization to the positive-reinforcing effects of cocaine in intact and sham-lesioned rats responding on a PR schedule of reinforcement. These effects were blocked completely in rats receiving small, discrete lesions of the dorsomedial frontal cortex, even though the three groups did not differ on measures of cocaine self-administration prior to the binge-abstinence history. These data suggest that the dorsomedial frontal cortex plays a critical role in either the development or expression of cocaine sensitization, which is believed to mediate, in part, the transition from casual drug use to compulsive drug use in human cocaine addicts. These findings, coupled with those from previous laboratory studies, suggest that the excitatory amino acid projections from the dorsomedial frontal cortex might be future targets of pharmacological treatments for cocaine dependence.

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