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Effect of 6-Hydroxydopamine Lesions of the Medial Prefrontal Cortex on Intravenous Cocaine Self-Administration Under a Progressive Ratio Schedule of Reinforcement

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McGREGOR, A., G. BAKER AND D. C. S. ROBERTS. *Effect of 6-hydroxydopamine lesions of the medial prefrontal cortex on intravenous cocaine self-administration under a progressive ratio schedule of reinforcement.* PHARMACOL BIOCHEM BEHAV **53**(1) 5–9, 1996.—Rats were trained to self-administer intravenous cocaine under a progressive ratio (PR) schedule of reinforcement. Under this schedule, an increasing number of lever responses had to be made to obtain each subsequent reinforcement (1.5 mg/kg per injection). Once stable responding was achieved with this schedule, bilateral 6-hydroxydopamine (6-OHDA) or vehicle-only injections were delivered into the medial prefrontal cortex (mPFC). Following recovery from surgery, the animals were given access to cocaine under the PR schedule. The effect of the lesion on self-administration behaviour was examined at various doses of cocaine (0.09–1.5 mg/kg per injection). 6-OHDA lesions of the mPFC had no effect on self-administration behaviour at the higher unit doses of cocaine. However, at the lower doses (0.09 and 0.19 mg/kg per injection), the lesion caused a significant increase in break point (BP), the number of responses made to obtain the last reinforcement of a self-administration session. The neurochemical results showed a significant reduction (57%) in mPFC levels of dopamine (DA) and 3,4-dihydroxyphenylacetic acid (DOPAC) (53%), with no changes in noradrenaline or serotonin levels. In contrast, the lesion caused no changes in DA or DOPAC levels in the nucleus accumbens (NACC) or striatum. These results indicate that the DAergic innervation of the mPFC cortex has a role in cocaine self-administration behaviour; however, whether this role is contingent on NACC DA function remains to be elucidated.

Cocaine Self-administration Medial prefrontal cortex 6-Hydroxydopamine Progressive ratio Reinforcement

CERTAIN aspects of the neural mechanisms underlying cocaine reinforcement and cocaine self-administration behaviour are now well established. In particular, a central role for dopamine (DA) and the nucleus accumbens (NACC) in drug reinforcement processes is widely documented. However, DAergic innervation of other mesocorticolimbic areas has also been implicated in the mediation of different aspects of cocaine's CNS actions.

In this regard, the medial prefrontal cortex (mPFC) is receiving increasing attention. This brain area not only receives a heavy DAergic innervation from the ventral tegmental area (VTA) (2,6,17,29), but also sends a heavy projection to the NACC (29,30). A role for the mPFC in cocaine reinforcement mechanisms has been implicated by the demonstration that rats will self-administer cocaine directly into the mPFC, and that this behaviour can be disrupted by co-administration of DA antagonists (7,8). More recently, the same authors have reported that self-administration of cocaine into the mPFC causes decreases in mPFC DA and concomitant increases in NACC DA turnover (9). An inhibitory influence of mPFC

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DA over various subcortical structures, including the NACC, has been previously considered (3,16). Thus, lesions of the mPFC have been shown to increase locomotor activity and the locomotor-inducing effects of amphetamine, both of which are thought to be mediated, at least in part, by the NACC (11). Such lesions have also been reported to increase DA levels and DA turnover in the NACC and striatum [(4,24); also see subsequent description).

However, the study of mPFC DA and intravenous psychostimulant self-administration behaviour has not produced a concurring set of results. Martin-Iverson et al. (18) trained rats to self-administer cocaine and then delivered 6-OHDA into the mPFC. The authors reported that such lesions increased DA turnover in the NACC, but had no effect on cocaine self-administration behaviour. Similarly, Lecesse and Lyness (15) investigated the effects of mPFC 6-OHDA lesions on amphetamine self-administration. These investigators reported no effect on self-administration behaviour, although there was an increase in DA turnover in the NACC. More recently, Schenk et al. (28) investigated the effects of 6-OHDA lesions of the mPFC on cocaine self-administration over a wide range of cocaine doses. These authors found that the lesion effects become apparent only when lower doses of cocaine were available. The lesion appeared to lower the threshold unit dose at which acquisition or maintenance of self-administration behaviour would occur. However, in contrast to previous studies, there was no change in NACC DA levels or DA turnover in this experiment.

Thus, to date, the data regarding the mPFC and its involvement in cocaine self-administration behaviour are not entirely consistent. The present study set out to reexamine the role of mPFC DA in cocaine self-administration. We used 6-OHDA lesions of the mPFC and tested a wide range of doses to parallel the experiment by Schenk et al. (28). In contrast, however, the present study employed a progressive ratio (PR) schedule of reinforcement rather then the fixed-ratio (FR) schedule previously employed in studies. This schedule can give a clearer indication of the change in direction of drug reinforcement efficacy when it occurs (25) and offers an alternative measure with which to investigate self-administration behaviour.

METHODS

Animals

Male Wistar rats (Charles River, Quebec, Canada), weighing 250-300 g at the start of the experiment, were used. Animals were housed under a reversed lighting schedule (lights off at 0900–2100 h) and given free access to food and water.

Self-Administration

Prior to entry into the self-administration experiment, animals were deprived of food for 24 h and trained to press a response lever for food reinforcement (45-mg Noyes pellet, Technolab Industries, Montreal) under an FR1 schedule. After completing two such training sessions with > 200 lever responses, an animal was accepted into the self-administration study.

Under barbiturate anaesthesia [pentobarbitol, 60 mg/kg, intraperitoneally (IP)], animals were implanted with a chronically indwelling jugular cannula that exited the back at the level of the scapula. The cannula was mounted on a counterbalanced swivel above a Plexiglas cage (25 × 25 × 25 cm), which allowed the animal free movement around the cage. Animals were given 24 h to recover from surgery.

Self-administration sessions were run daily for 5 h and were always initiated with a "priming" injection administered by the experimenter. Animals were trained to press the response lever under an FR1 schedule of cocaine reinforcement (1.5 mg/kg per 0.1-ml injection). A 20-s stimulus light positioned above the response lever accompanied the injection and signalled a timeout period during which no drug was available.

Once an animal had achieved 3 consecutive days of stable responding (±5%), the PR schedule of reinforcement was introduced. Under this schedule the animal was required to make a progressively greater number of responses to obtain each subsequent injection on a particular day. To earn a cocaine injection, the response requirement for each successive injection was increased in the following series: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, 737, and 901 [for details, see (26)]. The number of reinforcements earned before a 1-h period of nonreinforcement represented the breaking point (BP) reached in a self-administration session. After achieving 3 consecutive days of stable break points (±1 BP), the animal received a bilateral 6-OHDA lesion of the mPFC ($N = 6$) or a sham lesion ($n = 6$) (see subsequent description).

Surgery

Desipramine (Sigma, St. Louis, MO) (25 mg/kg, IP) was administered 30 min before surgery, to protect noradrenaline-containing terminals from the effects of 6-OHDA. All animals were anaesthetised with halothane and then placed in a Kopf (David Kopf Instruments, Tujunga, CA) stereotaxic apparatus (incisor bar: −3.3 mm). The scalp was retracted and bilateral holes were drilled in the skull above the injection sites. The needle of a 10-μl Hamilton syringe (Bonaduz, Switzerland) was lowered to the appropriate coordinate [AP: +3.0 mm from bregma; L: +0.7 mm; V: −3.5 mm; taken from (23)]. Injection of 6-OHDA (4 μg of freebase in 1 μl 0.9% saline and 0.2 μg/μl ascorbic acid) was then made over 5 min and the needle was left in place for a further 5 min. Sham lesions were made in an identical manner except that vehicle alone was injected. The scalp was then sutured closed and the animal was allowed 48 h recovery before being reintroduced into the self-administration sessions.

We studied the effects of the lesion on self-administration behaviour at five different unit doses of cocaine: 1.5, 0.75, 0.375, 0.19, and 0.09 mg/kg. Each animal had access to a particular dose for 4 consecutive days, before another dose was introduced. All the doses were made available in a counterbalanced fashion across animals. For the behavioural analysis, however, only the last 3 days of responding at each dose were used. When an animal was switched from one dose to another it often took 1 day for the animal to reestablish a stable response level at the new dose. Thus, by not using the 1st day of data, one produces a more accurate measurement of each particular animal's BP at any particular dose.

Biochemistry

Rats were decapitated and theirs brains removed and immediately dissected on ice. Brain tissue samples were frozen in liquid nitrogen and then stored at −70°C. The dissection included three areas: mPFC, NACC, and STRM.

After homogenising in ice-cold 0.1 N perchloric acid (0.05 M) containing EDTA (10 mg%), samples were centrifuged to remove precipitated protein, and the supernatants were used for analysis of DA, NA, 5-HT, and metabolites by high-performance liquid chromatography (HPLC) [see (1) for de-

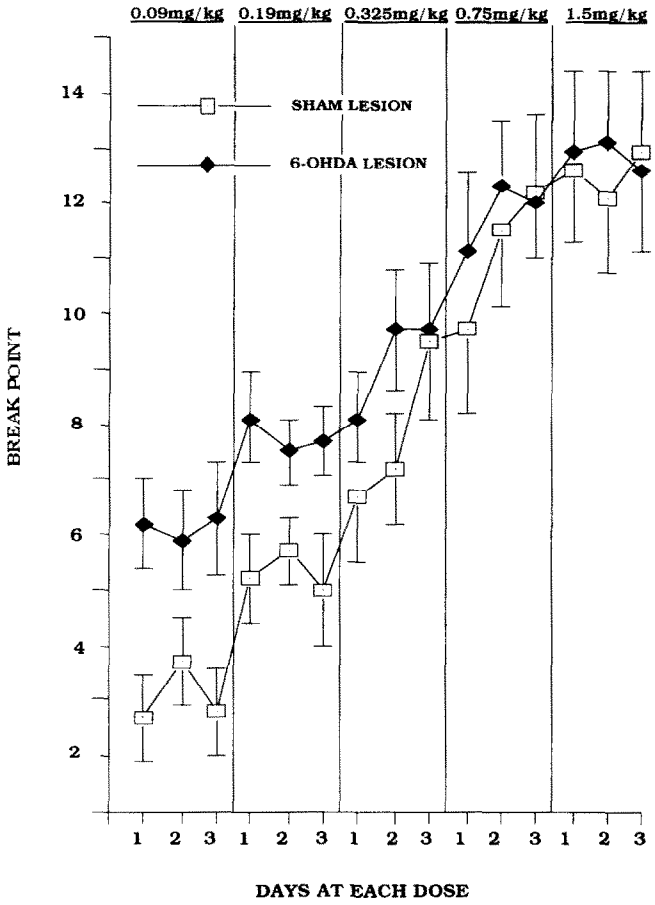

FIG. 1. Mean (±SEM) BP obtained following either 6-OHDA lesions or sham lesions of the mPFC at five doses of cocaine. Access to the different doses was organised in a Latin square design across animals. The separate partitions represent consecutive days at each dose but not the order of dose presentation.

tails). Briefly, the HPLC system consisted of a solvent delivery system (model 510; Waters Associates, Milford, MA) coupled to an automatic injector (WISP; Waters model 710B), Compounds were separated on a Spherisorb 5 ODA column (4.6 × 25 mm, 5 mm particle size; Phenomenex, Torrence, CA) fitted with a precolumn (4.6 × 30 mm). Eluants from the column were detected by an electrochemical detector (Model 460; Waters) with the applied potential set at 0.85 V. Chromotographic peaks were recorded and integrated using a model 740 integrator (Waters). The mobile phase for the HPLC system consisted of 55 mM $NaH_2PO_4 \cdot H_2O$, 0.73 mM octanesulfonic acid, 0.37 mM disodium EDTA, and 10% v/v acetonitrile; the pH value was adjusted to 3.0 with phosphoric acid.

Statistics

The behavioural data were analysed by two-way analysis of variance (ANOVA), with a between-subjects factor for lesion group and a within-subject factor for cocaine dose. The biochemical data were analysed with a one-way ANOVA using a between-subject design for each brain site.

RESULTS

Figure 1 shows the effects of 6-OHDA lesions of the mPFC on cocaine self-administration behaviour under a PR schedule of reinforcement. The ANOVA revealed no significant lesion effect [$F(1, 11) = 2.67, p < 0.13$], but there was a significant effect of cocaine dose [$F(4, 44) = 0.001, p < 0.01$] and a significant lesion × dose interaction [$F(4, 44) = 3.5, p < 0.01$]. As can be seen, at the higher cocaine doses (1.5, 0.75, and 0.375 mg/kg per injection) there was no effect of the lesion on BP; however, at 0.19 and 0.09 mg/kg per injection, post hoc comparisons of group means revealed that the lesion did produce a significant increase in BP (Newman-Keuls, $p < 0.05$).

Table 1 shows the results of the biochemical analysis of brain tissue levels of DOPAC and DA from the mPFC, STRM, and NACC. Relative to the sham control levels, there was a 57% reduction in mPFC DA and 53% reduction in mPFC DOPAC [$F(1, 11) = 14.3, p < 0.01$; $F(1, 11) = 12.6, p < 0.01$, respectively]. There were no other changes in DA or DOPAC levels in the structures dissected following the lesion (Table 1). Futhermore, there were no significant changes in either NA or 5-HT levels in any of the areas examined in this study (data not shown).

DISCUSSION

We found 6-OHDA lesions of the mPFC to produce effects on cocaine self-administration; but these effects depended on the unit injection dose of cocaine tested. Relative to sham-operated rats, animals depleted of mPFC DA responded to a higher BP when tested at low-unit injection doses of cocaine. However, the lesion had no effect on BP at higher unit doses of cocaine. This result indicates that DA depletion in the mPFC altered the reinforcing efficacy of near-threshold doses of cocaine without altering the reinforcing potency of the drug.

This result is in accord with a report by Schenk et al. (28), which demonstrated effects of similar lesions on cocaine self-administration behaviour under an FR schedule of reinforcement. These authors found that following mPFC 6-OHDA lesions, lower cocaine doses (comparabie to those used here) were capable of both maintaining and supporting self-administration behaviour acquistion, whereas responding for higher doses was unaffected by the lesion. The results from the present PR study thus confirm the work of Schenk et al. (28) and establish the fact that the effect seen under the FR

TABLE 1

MEAN ±SEM LEVELS (ng/g) OF DOPAMINE (DA) AND DOPAC IN THE MEDIAL PREFRONTAL CORTEX (MPFC), NUCLEUS ACCUMBENS (NACC) AND STRIATUM (STRM)

	MPFC	NACC	STRM
DA			
Sham	59.3 ± 4.4	2751 ± 456	9941 ± 230
Lesion	25.1 ± 1.1*	3062 ± 408	9175 ± 653
DOPAC			
Sham	41.2 ± 6.3	883 ± 89	1386 ± 30
Lesion	21.8 ± 3.4†	766 ± 121	1259 ± 114

Statistics are one-way ANOVA.
*$p < 0.001$, †$p < 0.05$, significantly different from sham-lesioned group.

schedule indeed reflected real increases in the reinforcing efficacy of low doses of cocaine following the lesion.

However, it is possible that these effects are not reinforcer-specific (i.e., not restricted to cocaine alone), and it remains to be seen whether DA deafferentation in the mPFC might also potentiate the reinforcing efficacy of other drugs and reinforcers, such as food or water. It should also be noted that the DA depletion achieved in the present study was rather low (57%). The high degree of protection achieved for NA-containing terminals in the mPFC suggests that some of the DA detected in the mPFC may in fact be present in NA-releasing terminals. Thus, it also possible that effects produced at the lower doses of cocaine represent a partial DA lesion effect, such that compensatory DAergic mechanims were induced. The reinforcing efficacy of low doses of cocaine could have been potentiated through this type of mechanism. However, because there was no change in NACC DA or DA turnover, this explanation seems less likely.

The data suggest that depletion of DA from the mPFC augments the reinforcing effects of lower doses of cocaine. This conclusion appears to be at variance with another line of evidence indicating that mPFC DA is not important in cocaine self-administration. 6-OHDA lesions of the mPFC have previously been shown to have no effect on cocaine (18) or amphetamine (15) self-administration behaviour. Both of these studies however, investigated a single, relatively high unit injection dose. If the effect of 6-OHDA lesions in this brain area is restricted to doses at or near threshold level, as indicated here, then these earlier results are in fact consistent with the present report. More difficult to resolve, however, is a series of studies using intracerebral injections to investigate the role of the mPFC in cocaine self-administration behaviour. Goeders and Smith (7,8) reported that rats will self-administer cocaine directly into the mPFC and that coinjection of the DA D_2 receptor antagonist sulpiride abolishes this behaviour. Furthermore, we recently reported that injections of the DA D_1 receptor antagonist SCH 23390 in the mPFC dose-dependently decreased the reinforcing effects of cocaine, as demonstrated by a decrease in BP and an increase in the rate of cocaine self-administration (19). Together, these data support the conclusion that the DA innervation of the mPFC serves some role in cocaine reinforcement mechanisms.

However, if DA terminals within the mPFC underlie some aspect of cocaine self-administration behaviour, why should DA lesions augment the behaviour? One possible explanation may lie in the type of DA manipulation employed. 6-OHDA lesions produce a chronic DA deafferentation of the mPFC, which may cause secondary changes in the neurochemistry of other brain regions. This may be especially true in animals chronically exposed to cocaine (14,31). Such discrepancies have also been produced following similar types of DA manipulation in the amygdala (20,21) and the striatum (Roberts and Koob, unpublished observations) of cocaine self-administering rats.

Numerous studies have found that 6-OHDA lesions of the mPFC induce increases in NACC and STRM DA turnover (4,10,15,18,24). However, in the present study the 6-OHDA lesion did not induce changes in NACC or STRM DA turnover, even though cocaine self-administration behaviour was affected. Similarly, others have reported that such lesions do not alter NACC or STRM DA levels or DA turnover (12,13, 22,28). More recently, it has been demonstrated that although they do not alter basal levels of NACC DA or turnover, 6-OHDA lesions of the mPFC can enhance the response elicited from NACC DA afferents. Thus, Deutch et al. (5) found that a mild stressor (i.e., foot-shock) that did not produce an enhanced DA release in the NACC of mPFC sham-lesioned rats was able to elicit such a neurochemical response in mPFC 6-OHDA-lesioned rats. In similarly prepared rats, Rosin et al. (27) reported that pharmacologic challenge with haloperidol increased tyrosine hydroxylase activity in the NACC of lesioned but not sham-lesioned animals. These results suggest that DA depletion in the mPFC can alter certain aspects of subcortical functioning, including DA responses in NACC to pharmacologic and environmental challenges of the system. Thus, it is possible that in the present study, 6-OHDA lesions of the mPFC altered DA function within the NACC to render this region sensitive to low doses of cocaine, which in the intact brain do not support robust self-administration behaviour. In accord with such an interpretation, Goeders and Smith (9) reported that intracranial self-administration of cocaine caused a decrease in DA turnover in the mPFC but an increase in DA turnover in the NACC. Together, the results suggest that decreased DA function within the mPFC can increase DAergic function within the NACC, and thus support cocaine self-administration behaviour either intravenously or intracerebrally in the mPFC.

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