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Both the shell of the nucleus accumbens and the central nucleus of the amygdala support amphetamine self-administration in rats

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Abstract

Intracranial self-administration of drugs offers the opportunity to localize the neuronal substrates mediating the rewarding effects of drugs. The purpose of the present study was to explore whether the nucleus accumbens shell and the central nucleus of the amygdala, two components of the "extended amygdala," would support self-administration of the psychostimulant amphetamine. Male Wistar rats were trained to lever press under a Fixed Ratio 1 schedule of reinforcement for D-amphetamine injections (0, 1.0, 1.5, 2.0 and 3.0 μg/μl/inj) into either the nucleus accumbens shell or the central nucleus of the amygdala. An ascending limb dose–response function with peak responding at the 2.0 μg/μl/inj dose was obtained for self-administration at both brain sites. These results indicate that monoaminergic transmission in both the nucleus accumbens shell and the central nucleus of the amygdala mediates the rewarding effects of amphetamine. Further, the present study provides additional evidence about the functional homogeneity of the forebrain continuum called the "extended amygdala." © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Nucleus accumbens shell; Central nucleus of the amygdala; Amphetamine; Psychostimulant; Intracranial self-administration; Reward; Rats

1. Introduction

Intracranial self-administration of amphetamine in rats is a useful tool for the identification of the components of brain reward circuits. Hoebel and coworkers (Hoebel et al., 1983; Parada et al., 1994) were one of the first groups to demonstrate that rats will self-administer amphetamine directly into the nucleus accumbens. Since then, it has been shown that several other drugs are self-administered by experimental animals into discrete brain sites. These drugs and sites include but are not limited to morphine (Bozarth and Wise, 1980) or ethanol (Gatto et al., 1994) into the ventral tegmental area, cocaine into the medial prefrontal cortex (Goeders and Smith, 1983, 1984), D-amphetamine into the orbitofrontal cortex of monkeys (Phillips et al., 1981), phencyclidine or dizolcipine [two *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonists] or 3-(2-carboxypiperazine-4-yl)propyl-1-phosphoric acid (CCP, a competitive NMDA receptor antagonist) into the nucleus accumbens shell or the frontal cortex (Carlezon and Wise, 1996) and carbachol (a nonspecific cholinergic receptor agonist; Ikemoto et al., 1998) or D-amphetamine (Phillips et al., 1994) into the core of the nucleus accumbens.

These and other findings are consistent with the hypothesis that the mesocorticolimbic dopaminergic system and its connections are part of the circuit that mediates the rewarding effects of drugs of abuse (Koob, 1992). Recently, there has been interest in exploring the potential role in drug reward of other brain systems that are anatomically linked and related to the mesolimbic system. A theoretical anatomical structure postulated to play a significant role in reward and motivation is the "extended amygdala" (Heimer and Alheid, 1991). Components of the extended amygdala include the shell of the nucleus accumbens, the central nucleus of the amygdala and the bed nucleus of the stria terminalis. These sites have cytoarchitectural similarities and similar afferent and efferent connections (Heimer and Alheid, 1991; however, see Zahm et al., 1999). In support of the above hypothesis is evidence indicating the functional homogeneity of the "extended amygdala." More specifically, administration of a dopamine D1 receptor antagonist into either the shell of the nucleus accumbens,

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the central nucleus of the amygdala or the bed nucleus of the stria terminalis blocked the acute rewarding effects of cocaine self-administration in rats (Caine et al., 1995; Epping-Jordan et al., 1998).

The purpose of the present study was to explore whether the nucleus accumbens shell and the central nucleus of the amygdala would support amphetamine self-administration in rats. The role of these two sites, and the central nucleus of the amygdala in particular, in psychostimulant reward has not been studied extensively using the intracranial self-administration methodology.

2. Methods

2.1. Subjects and surgery

Twelve male Wistar rats (Charles River, Kingston, NY), weighing 275–300 g at the start of the experiment, were housed in a temperature, humidity and light cycle-controlled vivarium on a reverse light/dark cycle (lights off at 10 am). Rats were tested at the same time each day during the dark phase of their cycle. Subjects were anaesthetized with 1.0–1.5% halothane/oxygen mixture and prepared with 10 mm, 23 G stainless-steel cannulae 3 mm above either the nucleus accumbens shell (AP +1.6, ML ±0.8, DV −4.7, flat skull; $n=6$) or the central nucleus of the amygdala (AP −2.56, ML ±4.2, DV −5.8, flat skull; $n=6$; Paxinos and Watson, 1998). The cannulae were secured with four skull screws and cemented with Langs dental acrylic (Co-Oral-Ite, Diamond Springs, California). In addition, an attachment consisting of a 3 mm O.D. threaded nylon rod, 8 mm in length, was cemented on the skull to provide a secure mechanical connection of the injection lead to the pump. All subjects were treated in accordance with the National Institutes of Health guide for the care and use of the laboratory animals, and animal facilities and experimental protocols were in accordance with the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC).

2.2. Apparatus

Five sound-attenuated Plexiglas operant conditioning chambers containing a 2 cm wide lever positioned 3 cm above the floor and 5 cm from the walls were used. The extension of the lever into the chamber indicated the initiation of a test session. Each apparatus was equipped with a microstepper motor pump (Hesse et al., 1997) that allowed for fast intracranial delivery of an amphetamine solution contingent upon the subject's lever press response. The micropump consisted of a screw drive mechanism driven by a stepper motor and moved fluid by direct displacement. The pump generated sufficient pressure to maintain the desired output, even in the event of blockade from deposits at the end of the intracerebral injection tip. Polyethylene tubing ending in an injector tip (30 G) was attached to the piston. The tubing was protected with a length of metal spring to prevent the subject from chewing the lead. The subject was further attached with a dummy lead to the threaded anchor so that the injector tip stayed in place throughout the duration of each test session. Hence, the rats could move freely about the chamber. The operant conditioning chambers were operated by a microcontroller connected to a microcomputer that determined all session and data collection functions.

2.3. Experimental procedures

The subject was connected to the apparatus by inserting a 13 mm (for the nucleus accumbens site) or 14 mm (for the central nucleus of the amygdala site) injector into one of the cannulae and then screwing on the dummy lead to the threaded anchor. Rats were initially given access to 2.0 μg/μl/inj of D-amphetamine sulfate (Research Biochemicals, Natick, MA) solution delivered over 1 s. Subjects were allowed to self-train. If animals did not self-train within 5 days, the contralateral brain site was used on subsequent days. Animals that failed to self-administer in either site were not used in the study. Histologies of all subjects' brains were examined (see below). The amphetamine was dissolved in artificial cerebrospinal fluid (8.4738 g NaCl, 145 mM; 0.2088 g KCl, 2.8 mM; 0.2440 g Mg_2C1, 1.2 mM; 0.1764 g Ca_2Cl, 1.2 mM; 0.9693 g D-glucose, 5.4 mM; solvent was Nanopure water; solution was at 7.2–7.4 pH; Parsons et al., 1996). Each lever press resulted in the delivery of an amphetamine infusion and the illumination of a light positioned above the lever. The light remained lit throughout the duration of the infusion and the subsequent 20 s time-out period. Responses during the time-out period were recorded but had no programmed consequences. Each testing session was 2 h in duration. Testing at the 2.0 μg/μl/inj dose took approximately 1 week to reach stable baseline responding (defined as five or more responses per session and less than 10% variation over three daily testing sessions). Then, rats were given access to a range of D-amphetamine sulfate doses (1.0, 1.5 and 3.0 μg/μl/inj) presented in a random order. Each dose was available for 3 consecutive test days. In addition, two rats with cannulae in the amygdala and one rat with cannulae in the nucleus accumbens were given access to the 0 μg/μl/inj dose (i.e., aCSF only) for 3 consecutive days, which was presented in a random order together with the other three doses. No priming injections were given at any time during the experiment.

2.4. Statistical analyses

First, data from rats with nucleus accumbens and amygdala placements were analyzed separately. The mean number of responses on the second and third days for the 1.0, 1.5 and 3.0 μg/μl/inj amphetamine doses and the last 2 days for the 2.0 μg/μl/inj training dose were calculated. Note that the 0 μg/μl/inj dose data were not included in the analyses

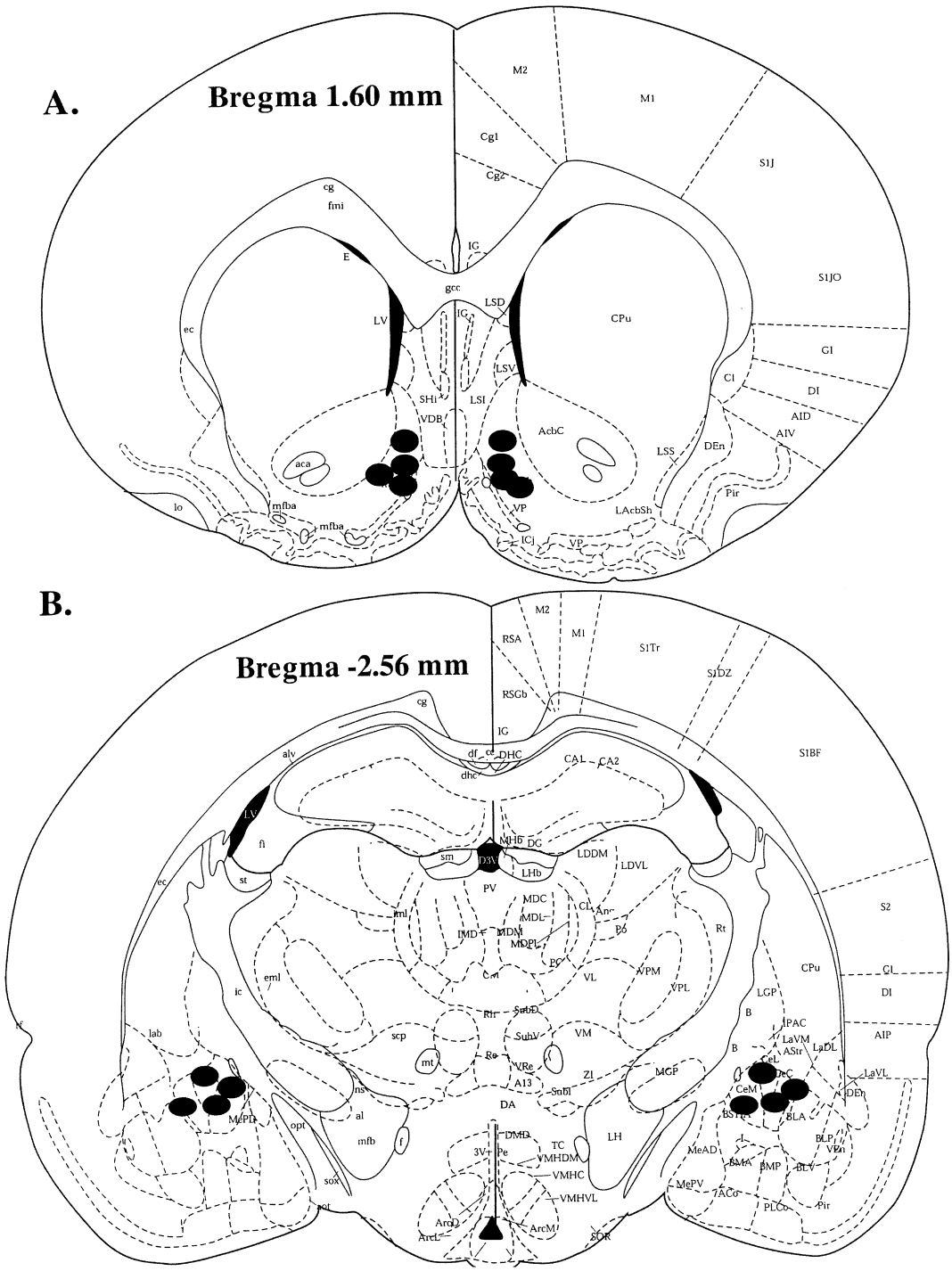

Fig. 1. Circles indicate the sites of D-amphetamine injection that were in either the shell of the nucleus accumbens (A), or the central nucleus of the amygdala (B). Plates are taken from the Paxinos and Watson's Brain Atlas (Paxinos and Watson, 1998).

because not all subjects were tested under this condition. Statistical tests for the sphericity assumption (Anderson, 1958) indicated nonhomogeneity of variance for the data of either group of rats ($P < .05$). Thus, data were analyzed using nonparametric statistical tests (Siegel, 1956). First, the Friedman two-way analysis of variance (ANOVA) by rank was performed. Statistically significant effects in the Friedman test were followed by pairwise comparisons using the Wilcoxon Pair Test. Second, due to the small differences between the dose–response functions for the two groups that would require large sample sizes to detect statistically reliable differences between the two sites (Cohen, 1988), data from the shell of the nucleus accumbens and the central nucleus of the amygdala were combined and analyzed as

described above. Time-out responses were analyzed using a one-way repeated-measures ANOVA, with amphetamine dose as the within-subject factor, and collapsed across the two sites. Parametric tests were conducted using the BMDP Statistical Software Package (Dixon, 1992). Nonparametric statistical tests were conducted using the Prism Graphpad software package (copyright 1996). Criterion for significance was set at the .05 level.

3. Results

Twelve animals underwent surgical implants of bilateral cannulae. Two of the rats with intended amygdala placements lost their head mounts early during training, and two with intended nucleus accumbens shell placements failed to self-train. Of the two rats that failed to reach criterion, one rat's cannula was positioned into the nucleus accumbens core (the other cannula of this subject was never used because of blockage). The other rat had correctly placed cannulae in the shell of the nucleus accumbens but nevertheless failed to achieve criterion level of responding probably because of an infection at the base of its cannulae. Thus, there were four animals per group that provided the reported data. The injection sites for these eight subjects that had accurate placements in either the shell of the nucleus accumbens or the central nucleus of the amygdala are depicted in Fig. 1. The Friedman ANOVA indicated that there was a main effect of dose ($\chi^2 = 1723.5$, $df = 3$, $P < .001$), not specific to site. Post hoc comparisons indicated that responding for the 2.0 μg/μl/inj dose was higher than responding for the 1.0 ($P < .01$) and 1.5 μg/μl/inj doses ($P < .05$), but not from the 3.0 μg/μl/inj dose (Fig. 2). The three animals that had access to the 0 μg/μl/inj dose (aCSF only) emitted 1.33 ± 0.382 (range 0.5–2.0) responses over the last two out of the three days that the rats had access to aCSF. Because not all animals had access to the 0 μg/μl/inj dose, the 0 μg/μl/inj data were not included in the analyses. There were minimal number of responses during the 20 s time-out period that remained the same throughout the experiment independent of amphetamine dose available to the subjects [$F(3,21) = 0.68$; n.s.; see Table 1].

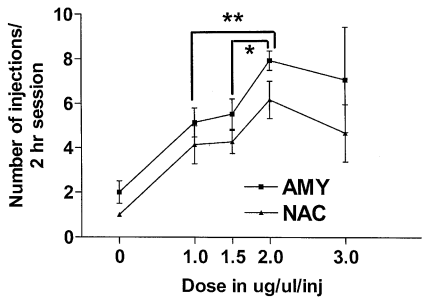

Fig. 2. Dose–response functions for unilateral D-amphetamine self-administration directly into the central nucleus of the amygdala or the shell of the nucleus accumbens of rats. Values represent mean number of responses (± S.E.M.) over 2 days on each dose. Mean and standard error of the mean for the 0 μg/μl/inj dose are from three subjects (two amygdala and one nucleus accumbens placement). Asterisks indicate statistically significant differences between the 2.0 μg/μl/inj dose and the 1.0 and 1.5 μg/μl/inj doses when data from the two groups were combined (* $P < .05$, ** $P < .01$). Note that data from the two sites are presented separately, but analyses and asterisks show significance when the amygdala and accumbens data were combined.

Table 1
Mean ± standard error of the mean (S.E.M.) time-out responses for animals self-administering various doses of D-amphetamine in either the central nucleus of the amygdala (AMY) or the nucleus accumbens shell (NAC)

	D-Amphetamine dose				
Brain site	0 μg/μl	1.0 μg/μl	1.5 μg/μl	2.0 μg/μl	3 μg/μl
AMY	1 ± 0.41	0.88 ± 0.6	1 ± 0.67	1.4 ± 0.28	1.13 ± 0.76
NAC	2 ± 0	0.25 ± 0.29	0 ± 0	0.38 ± 0.43	0.13 ± 0.14

4. Discussion

Both the shell of the nucleus accumbens and the central nucleus of the amygdala supported amphetamine self-administration in a dose-dependent manner as indicated by the dose–response functions shown in Fig. 2. Further, subjects appeared to regulate/titrate their intake as a function of dose and time elapsed since the previous injection (see Fig. 3). An ascending limb dose–response function was obtained with peak responding occurring at the 2.0 μg/μl/inj D-amphetamine dose for both the nucleus accumbens shell and the central nucleus of the amygdala injection sites. Such a gradual ascending limb function has been observed previously with self-administration of other drugs, such as cocaine (e.g., Caine and Koob, 1995). It is possible that availability of higher amphetamine doses in the present study may have resulted in a descending limb of the curve. The results suggest that monoaminergic neurotransmission in either of these two brain sites mediates the acute rewarding effects of psychostimulant drugs.

The fact that both the nucleus accumbens shell and the central nucleus of the amygdala support amphetamine self-administration provides further evidence for the functional homogeneity of the extended amygdala. Recent anatomical analyses suggest that the shell of the nucleus accumbens, the central nucleus of the amygdala and the bed nucleus of the stria terminalis are components of a much larger forebrain structure, the "extended amygdala," which was identified in several species including humans and rats (e.g. Heimer et al., 1985; Heimer and Alheid, 1991; de Olmos et al., 1985).

This concept of an "extended amygdala" is based on observations that the components of these brain regions share common cell morphology, histochemistry, catecholamine innervation and peptide distribution, as well as common afferent and efferent projections. The hypothesis is that the extended amygdala may be involved in emotion and motivation (Heimer and Alheid, 1991) and, thus, in drug dependence. Previous studies have supported the

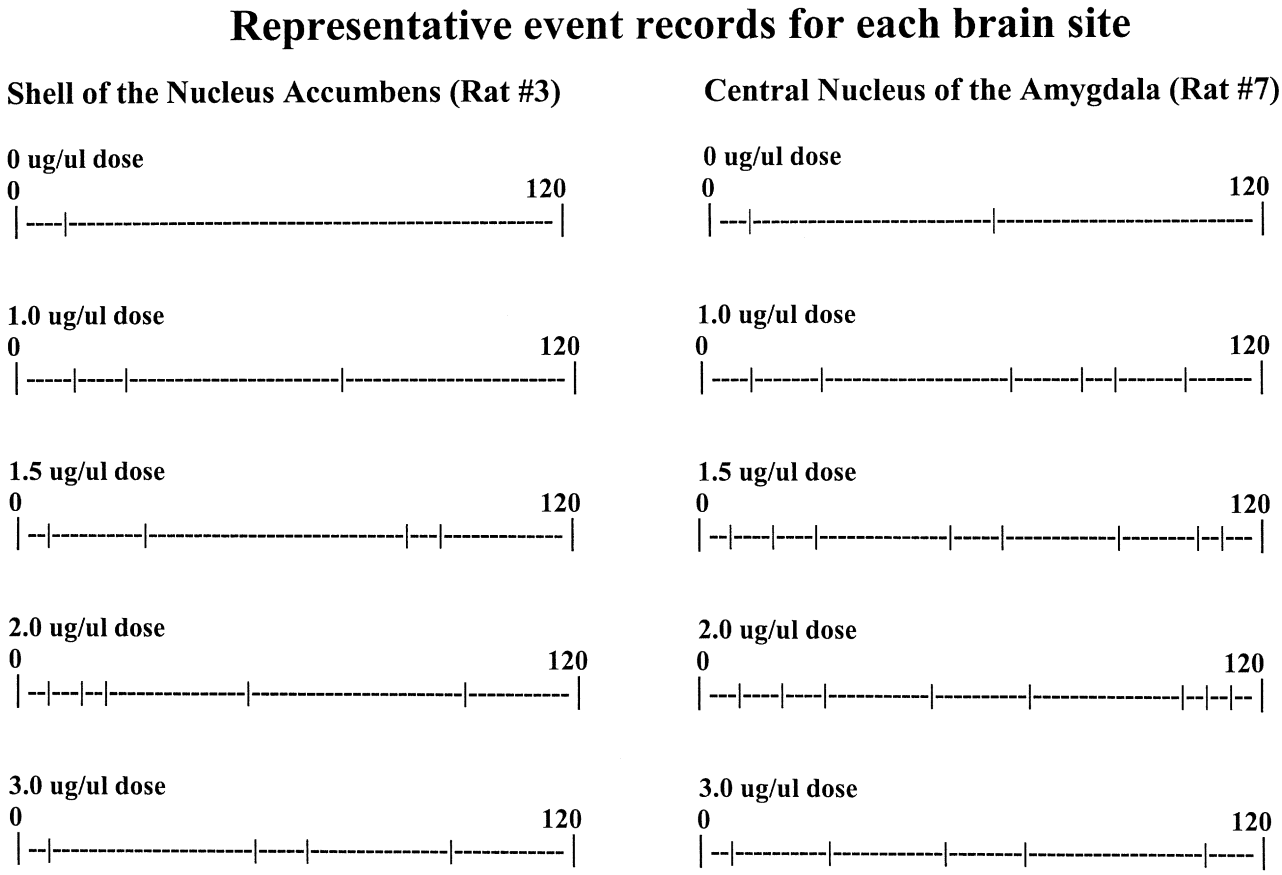

Fig. 3. Representative event records for two rats, one with placement in the shell of the nucleus accumbens (on the left) and one with placement in the central nucleus of the amygdala (on the right) for all doses tested (0, 1.0, 1.5, 2.0 and 3.0 μg/μl/inj). Tick marks represent self-administration infusions of D-amphetamine during the 2 h session.

functional homogeneity of anatomical components of the "extended amygdala" by indicating that injections of a D1 dopamine antagonist into either of three compartments of the "extended amygdala" (nucleus accumbens shell, central amygdala and bed nucleus of the stria terminalis), but not into other sites (caudate putamen, sites dorsal to the bed nucleus and lateral ventricle), attenuated the reinforcing effects of self-administered cocaine (Caine et al., 1995; Epping-Jordan et al., 1998). Most recent findings indicated that microinjections of an opioid receptor antagonist into the bed nucleus of the stria terminalis decreased heroin self-administration (Walker et al., 2000). Finally, the present data demonstrate that two components of the "extended amygdala" support self-administration of amphetamine.

The results of the present study are consistent with previously reported findings indicating that D-amphetamine is readily self-administered by rats into the area of the nucleus accumbens. Hoebel et al. (1983) showed that rats self-administered unilaterally approximately 40–50 injections of 0.65 μg D-amphetamine (dissolved into the 0.065 μl saline) per hour under a FR1 schedule of reinforcement. It does not appear that there was a time-out period after each injection. In the Hoebel study, the rates of self-administration were higher than those observed here and may be attributable to several methodological differences between the studies. In the present study, male Wistar rats were used, while female Sherman or female Sprague–Dawley rats were used in the Hoebel study. In the present study, higher amphetamine doses and larger injection volumes were used compared to the Hoebel study.

Further, in the present study, injection sites were confined to the area of the nucleus accumbens shell, while injection sites were not only in the shell but also along the medial part of the nucleus accumbens core extending just ventral to the lateral ventricle in the Hoebel study. It is possible that injection sites close to the ventricle allowed diffusion of amphetamine into the ventricle that led to higher response rates. The above speculation is supported by the high variability in response rates among subjects and was suspected by the authors to be the cause of an abrupt two- to threefold increase in response rates for few subjects in the middle of the study (Hoebel et al., 1983).

Another report by Phillips and coworkers indicated that amphetamine (1 μg/μl/inj/site) is readily self-administered by male Lister–Hooded rats into the nucleus accumbens core bilaterally under an FR1 TO 60 s schedule of reinforcement during 30 min sessions (Phillips et al., 1994). Animals were allowed to self-administer 10 injections or for

30 min, whichever occurred sooner. Data are presented only as response rates per minute excluding the time-out periods. Given the schedule in effect and the format of the data presentation, it is impossible to determine how many injections the rats self-administered and to directly compare with either the Hoebel or the present study. It appears, however, that response rates in the Phillips study were higher than those in the present study for the same total amphetamine dose (unilateral or bilateral). The higher rates may be attributable to (a) the bilateral injections being more reinforcing than the unilateral injections for the same total dose and (b) the fact that Lister–Hooded rats exhibit higher rates of responding and higher intake of psychostimulant drugs (i.e., cocaine) than Wistar or Long–Evans–Hooded rats (e.g., Markou and Koob, 1991; Markou et al., 1999; Semenova and Markou, 2000). Further, the lower rates observed in the present study compared to the Hoebel and Phillips studies may be due to the testing frequency. That is, in the present study, rats were tested every second day while tested only biweekly in the Hoebel and Phillips studies. As reported by Phillips, Hoebel and other authors (Hoebel et al., 1983; Phillips et al., 1994; Goeders and Smith, 1987), intracranial self-administration of drugs can be less problematic when the subjects have infrequent access to drug self-administration. Nevertheless, the present findings demonstrated that frequent self-administration sessions (i.e., every second day) led to reliable self-administration, although at lower rates than less frequent access to the drug. In conclusion, the higher response rates reported by Hoebel and Phillips compared to the response rates reported here are probably attributable to the different strain and sex of rats, injection sites, doses, injection volumes and vehicles used, bilateral versus unilateral injections and the frequency of the self-administration sessions.

Although in the present study only one lever was available in the operant conditioning chamber, it is rather unlikely that responses on the active lever reflected nonspecific amphetamine-induced activation because of the regularity (i.e., titration) of amphetamine intake (see Figs. 2 and 3). Further, previous studies investigating amphetamine and neurotensin self-administration directly into the nucleus accumbens and the ventral tegmental area, respectively, indicated clear discrimination by the animals between the active and inactive levers (Glimcher et al., 1987; Hoebel et al., 1983; Phillips et al., 1994). Finally, the present data indicate that the micropump used in the present study is an improvement in intracranial drug delivery systems because it allows for rapid and reliable delivery of predetermined drug doses in the nanoliter volume range into discrete brain regions (Hesse et al., 1997). The precision of the micropump delivery is demonstrated by the orderly set of data, the small standard error of the means and the precise titration of drug intake by the subjects seen in the present study that mimic intravenous self-administration dose–response functions (Carlezon and Wise, 1996).

In conclusion, using a new micropump delivery system, data were collected indicating that both the nucleus accumbens shell and the central nucleus of the amygdala support psychostimulant self-administration in rats. Finally, these data demonstrate the functional homogeneity of the extended amygdala.

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References

Anderson TW. An introduction to multivariate statistical analysis. New York: Wiley, 1958.

Bozarth MA, Wise RA. Electrolytic microinfusion transducer system: an alternative method of intracranial drug application. J Neurosci Methods 1980;2:273–5.

Caine SB, Koob GF. Pretreatment with the dopamine agonist 7-OH-DPAT shifts the cocaine self-administration dose–effect function to the left under different schedules in the rat. Behav Pharmacol 1995;6:333–47.

Caine SB, Heinrichs SC, Coffiin VL, Koob GF. Effects of the dopamine D-1 antagonist SCH 23390 microinjected into the accumbens, amygdala or striatum on cocaine self-administration in the rat. Brain Res 1995; 692:46–57.

Carlezon B, Wise RA. Rewarding actions of phencyclidine and related drugs in nucleus accumbens shell and frontal cortex. J Neurosci 1996;16:3112–22.

Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates Publishers, 1988.

de Olmos J, Alheid GF, Beltramino C. The rat nervous system. In: Paxinos G, editor. Amygdala. New York, NY: Academic Press, 1985. pp. 223–334.

Dixon WJ, editor. BMDP statistical software package. Los Angeles: University of California Press, 1992.

Epping-Jordan MP, Markou A, Koob GF. The dopamine D-1 receptor antagonist SCH 23390 injected into the dorsolateral bed nucleus of the stria terminalis decreased cocaine reinforcement in the rat. Brain Res 1998;784:105–15.

Gatto GJ, McBride WJ, Murphy JM, Lumeng L, Li TK. Ethanol self-infusion into the ventral tegmental area by alcohol-preferring rats. Alcohol 1994;11:557–64.

Glimcher PW, Giovino AA, Hoebel BG. Neurotensin self-injection in the ventral tegmental area. Brain Res 1987;403:147–50.

Goeders NE, Smith JE. Cortical dopaminergic involvement in cocaine reinforcement. Science 1983;221:773–5.

Goeders NE, Smith JE. Parameters of intracranial self-administration of cocaine into the medial prefrontal cortex. NIDA Res Monogr 1984; 55:132–7.

Goeders NE, Smith JE. Intracranial self-administration methodologies. Neurosci Biobehav Rev 1987;11:319–29.

Heimer L, Alheid GF. Piecing together the puzzle of the basal forebrain anatomy. In: Napier TC, Kalivas PW, Hanin I, editors. The basal forebrain: anatomy to function. New York: Plenum, 1991. pp. 1–41.

Heimer L, Alheid GF, Zaborszky L. The basal ganglia. In: Paxinos G, editor. The rat nervous system. Sydney: Academic Press, 1985. pp. 37–74.

Hesse GW, Stellar JR, Chevrette J. A simple and reliable method for delivering small fluid volumes to the brain of a freely moving rat. J Neurosci Methods 1997;72:35–8.

Hoebel BG, Monaco AP, Hernandez L, Aulisi EF, Stanley BG, Lenard L. Self-injection of amphetamine directly into the brain. Psychopharmacology 1983;81:158–63.

Ikemoto S, Glazier BS, Murphy JM, McBride WJ. Rats self-administer carbachol directly into the nucleus accumbens. Physiol Behav 1998; 63:811–4.

Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci 1992;13:177–84.

Markou A, Koob GF. Postcocaine anhedonia: an animal model of cocaine withdrawal. Neuropsychopharmacology 1991;4(1):17–26.

Markou A, Arroyo M, Everitt BJ. Effects of contingent and non-contingent cocaine on drug-seeking behavior measured using a second-order schedule of cocaine reinforcement in rats. Neuropsychopharmacology 1999;20:542–55.

Parada MA, Puig de Parada M, Hoebel BG. A new triple-channel swivel for fluid delivery in the range of intracranial (10 nl) and intravenous (100 μl) self-administration volumes and also suitable for microdialysis. J Neurosci Methods 1994;54:1–8.

Parsons LH, Caine SB, Sokoloff P, Schwartz JC, Koob GF, Weiss F. Neurochemical evidence that postsynaptic nucleus accumbens D3 receptor stimulation enhances cocaine reinforcement. J Neurochem 1996;67: 1078–89.

Paxinos G, Watson C. The rat brain in stereotaxic coordinates. 4th ed. San Diego: Academic Press, 1998.

Phillips AG, Mora F, Rolls ET. Intracerebral self-administration of amphetamine by rhesus monkeys. Neurosci Lett 1981;24:81–6.

Phillips GD, Robbins TW, Everitt BJ. Bilateral intra-accumbens self-administration of D-amphetamine: antagonism with intra-accumbens SCH-23390 and sulpiride. Psychopharmacology 1994;114:477–85.

Semenova S, Markou A. Cocaine-seeking behavior during withdrawal in rats. Soc Neurosci Abstr 2000;26:1305.

Siegel S. Nonparametric statistics for the behavioral sciences. New York: McGraw-Hill, 1956.

Walker JR, Ahmed SH, Gracy KN, Koob GF. Microinjections of an opiate receptor antagonist into the bed nucleus of the stria terminalis suppress heroin self-administration in dependent rats. Brain Res 2000;854:85–92.

Zahm DS, Jensen SL, Williams ES, Martin JR. Direct comparison of projections from the central amygdaloid region and nucleus accumbens shell. Eur J Neurosci 1999;11:1119–26.