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Differential effects of excitotoxic lesions of the amygdala on cocaine-induced conditioned locomotion and conditioned place preference

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Abstract. The reinforcing properties of cocaine can readily become associated with salient environmental stimuli that acquire secondary reinforcing properties. This type of classical conditioning is of considerable clinical relevance, as intense drug craving can be evoked by the presentation of stimuli previously associated with the effects of cocaine. Given the large body of evidence that implicates the amygdaloid complex in the learning of stimulus-reward associations, the present experiments examined the effects of quinolinic acid lesions of the amygdala on cocaine-induced conditional locomotion and conditioned place preference (CPP). Destruction of the amygdala did not affect basal or cocaine-induced locomotion, suggesting that the amygdala does not mediate the unconditioned psychomotor stimulant effects of this drug. Preconditioning lesions also failed to affect cocaine-induced conditional locomotion. Specifically, exposure of both lesioned and non-lesioned rats to a cocaine-paired environment produced significant conditional increases in locomotion. This lack of effect was contrasted by a complete blockade of cocaine-induced CPP by the amygdaloid lesions. These data demonstrate that cocaine-induced stimulus-reward conditioning can be differentially affected by lesions of the amygdala.

Key words: Amygdala – Classical conditioning – Cocaine – Conditioned place preference – Conditioned locomotion – Substance abuse

A significant clinical feature of cocaine abuse is the occurrence of environmentally cued craving (Gawin 1991; O'Brien et al. 1992). These conditioned cravings are the product of the repeated pairing of objects, places or events with the administration of cocaine and its subsequent euphoric effects. This phenomenon is of major significance with respect to cocaine's abuse potential, as these conditioned cravings can be intense, and can result in previously abstinent abusers resuming the use of cocaine, often despite concerted efforts by the addict to abstain from drug use (Gawin 1991; O'Brien et al. 1992). This clinical observation is supported by a number of laboratory studies that have demonstrated that cocaine's behavioral effects can readily become classically conditioned with specific environmental stimuli (Tatum and Seevers 1929; Barr et al. 1983; Stewart et al. 1984; Brown et al. 1992). Given the prevalence and clinical significance of these conditioned responses, a better understanding of the neurobiology of this phenomenon may assist in the development of more rational treatments for cocaine abuse.

There is a large body of evidence implicating the mesolimbic dopamine (DA) system in the reinforcing properties of some drugs of abuse (Roberts et al. 1977, 1989; Lyness et al. 1979; Fibiger and Phillips 1987; Di Chiara and Imperato 1988) and it has been suggested that conditioned stimuli associated with drug administration may also produce increases in dopaminergic transmission (Stewart et al. 1984). Although some studies have provided evidence that the mesolimbic DA system is involved in the conditional response to stimulants (Gold et al. 1988; Drew and Glick 1990), findings by other investigators suggest that the expression of the conditioned responses to psychomotor stimulants is DA-independent (Beninger and Hahn 1983; Beninger and Herz 1986; Weiss et al. 1989; Carey 1992). A recent study from this laboratory did not find any evidence for a conditional increase in DA release in the nucleus accumbens in response to the presentation of a drug paired environment (Brown and Fibiger 1992). This is consistent with an absence of evidence for conditioned dopaminergic activity following conditioning with a variety of agents such as cocaine (Barr et al. 1983), fentanyl (Finlay et al. 1988), morphine (Walter and Kuschinsky 1989) and apomorphine (Möller et al. 1987). Although the findings of these studies indicated an absence of conditional DA release, all found significant conditioned behavioral changes.

Recently, it has been reported that exposure to a cocaine-paired environment produces a conditional in-

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crease in c-fos expression in various forebrain limbic regions, such as the cingulate cortex, claustrum, lateral septal nucleus and the amygdala (Brown et al. 1992). In agreement with our previous neurochemical findings, no conditional activation was observed in the nucleus accumbens. Taken as a whole these data suggested that cocaine-induced conditioned locomotion is associated with increased neuronal activation within various forebrain limbic structures known to be involved in emotion and learning (Pascoe and Kapp 1985; Lopez da Silva et al. 1990; Powell et al. 1990; Thomas et al. 1991; Davis 1992). Consequently, it is possible that this specific form of classical conditioning involves similar neural circuits as other forms of learning (Mishkin and Aggleton 1981).

Of the areas exhibiting an increase in Fos positive neurons, the amygdala may be of particular importance. A large body of evidence suggests that amygdaloid nuclei are involved in stimulus-reward associations (Weiskrantz 1956; Jones and Mishkin 1972; Mishkin and Aggleton 1981; Gaffan and Harrison 1987; Cador et al. 1989; Everitt et al. 1991; Hiroi and White 1991; Kentridge et al. 1991). Furthermore, Post et al. (1988) have reported that although lesions of the amygdala (electrolytic and 6-hydroxydopamine) do not affect cocaine-induced hyperactivity they greatly attenuate environment-specific cocaine sensitization. Given these findings, the present study investigated the role of the amygdala in cocaine-induced conditional locomotion and cocaine-induced conditioned place preference (CPP). As previous studies have demonstrated that damage to fibres of passage within the amygdaloid complex produces behavioral effects that are unrelated to destruction of the amygdala (Riolobos and García 1987; Dunn and Everitt 1988), lesions were made using the fibre-sparing excitotoxin quinolinic acid.

Materials and methods

Subjects and drugs. Subjects were 66 male Long Evans rats (Charles River, Quebec), weighing 270–310 g at the beginning of the experiments. The rats were group housed (three per cage), on a 12-h light/12-h dark cycle (lights on 08:00 hours), with food and water available ad libitum. All subjects were handled periodically for 1 week prior to surgery. All experimental procedures were conducted at approximately the same time each day, during the animals' light phase.

Both cocaine hydrochloride (10 mg/kg, dissolved in isotonic saline, BDH) and 0.9% saline were injected IP in a volume of 1 ml/kg. The dose of cocaine is expressed as the weight of the salt.

Surgical procedure. Subjects were anaesthetized with sodium pentobarbital (50 mg/kg, IP; BDH) and xylazine (5 mg/kg, IP; Haver) and mounted in a stereotaxic frame (incisor bar: + 5.0 mm; David Kopf). Bilateral lesions of the amygdala were produced by the infusion of 0.5 µl quinolinic acid (0.12 M, in phosphate buffer, pH 7.1–7.4; RBI) at each of four injection sites (AP: +0.2 and −0.8 mm; ML: ±4.7 mm; DV: −7.9 from dura, relative to bregma; Pellegrino et al. 1979). Control subjects received 0.5 µl infusions of phosphate buffer (0.2 M, pH 7.4). Infusions were made through 30-gauge stainless steel cannulae attached to pump driven (Harvard Apparatus) 5 µl syringes (Hamilton) by PE-10 tubing (Clay Adams). All infusions were made at a rate of 0.1 µl/min, and cannulae remained at the injection site for an additional 5 min following the injection to allow for the diffusion of the excitotoxin. Solutions of quinolinic acid were prepared immediately prior to each infusion to ensure the potency of the excitotoxin. Following the removal of the cannulae, topical antibiotic (Rifocin, Lepetit) was applied to the wound and the incision was sutured with 4–0 silk. To reduce potential postoperative hypophagia and hypodipsia, the liquid diet Sustacal (Mead Johnson) was made available to all subjects for 7–10 days following surgery. During the 3–4 week postoperative recovery period subjects were handled daily. Subjects that exhibited spontaneous seizures or failed to resume normal feeding were sacrificed with sodium pentobarbital (100 mg/kg, IP).

Apparatus. Six circular (61 cm diameter) activity cages (BRS/LVE), each transected by six infrared beams, were used to measure locomotor activity during the training and testing of subjects in the cocaine-induced conditioned locomotion experiment. Photocell beam interruptions occurring more than 0.5 s apart were recorded with a NOVA IV (Data General) minicomputer equipped with MANX (GC Controls) software and interface.

Place preference conditioning was conducted in four identical shuttle boxes (80 × 25 cm, 35 cm high). Each box was divided into two compartments (34 × 25 cm) joined by a tunnel (8 × 8 × 6 cm) that could be closed at both ends by guillotine doors. The two compartments differed in the appearance of the walls and the type of floor (solid brown walls and a 1.2 cm wire mesh floor versus walls with black and white strips 1 cm wide and a floor of parallel bars spaced 1.2 cm apart). Translucent Plexiglas lids allowed a moderate amount of light from overhead incandescent lights to enter each compartment. Each shuttle box was mounted on a fulcrum, allowing its position to be detected by microswitches. The time spent in each compartment was recorded with dedicated electronic equipment. A more detailed description of this procedure, as well as dose-response data for cocaine-induced CPP, have been published previously (Brown et al. 1991).

Procedure. The effect of excitotoxic lesions of the amygdala on the classical conditioning of the locomotor stimulant effects of cocaine to a specific environment was examined in the first experiment. Both lesion and control rats were randomly assigned to one of three groups: conditioned, pseudoconditioned or control. Conditioned subjects were injected with cocaine (10 mg/kg, IP) and then placed into one of the circular activity cages for 30 min. After the training session, subjects were returned to their homecages, where they were injected with saline (1 ml/kg, IP) 4 h later. Pseudoconditioned rats were exposed to an identical procedure except that the order of administration of cocaine and saline was reversed. Specifically, these subjects were injected with saline prior to being placed in the activity cages and later with cocaine in their homecages. Control subjects were exposed to the same procedure as the other groups, except that they were injected with saline in both environments and never received cocaine. Each subject was assigned to a particular locomotor cage for the duration of the experiment. Training was conducted daily for 10 days at approximately the same time each day. On the test day (48 h after the final training session), subjects were placed in the locomotor cages and activity was monitored for 30 min. No injections were given on the test day.

Following completion of the conditioned locomotion experiment, both the lesioned and non-lesioned control (i.e. drug naive) subjects were tested for cocaine-induced CPP. The procedure for CPP consisted of three phases: habituation, conditioning and test. During the 3-day habituation phase, rats were placed in one of the compartments of the shuttle box (hereafter referred to as the start side), following a counterbalanced design. Following placement in the start side, and with both guillotine doors raised, the rats were given access to both compartments during the 900-s trial. During each trial, the time spent in each compartment was recorded. The conditioning phase was conducted over the next 8 days. On days 1, 3, 5 and 7, rats were given cocaine injections (10 mg/kg, IP) and immediately confined to the non-start side for 30 min. On alternate days, rats were injected with saline and confined to the start side for 30 min. On the test day, each rat was placed in the start-side and was given access to both compartments; the time spent in each compartment was recorded. No injections were given on the test day.

Histology. Following the completion of the second experiment, the subjects were deeply anaesthetized with sodium pentobarbital (100 mg/kg, IP) and transcardially perfused with isotonic saline followed by 4% paraformaldehyde in phosphate-buffered (0.1 M) saline. Following the perfusion, brains remained in 4% paraformaldehyde for 24–48 h before being transferred to a solution of 10% dimethylsulfoxide and 0.02% Na azide in Na phosphate buffer (0.1 M) for 48–72 h. Coronal sections of 50 μm were cut on a freezing microtome and every fourth section was mounted on chrome-alum coated slides and stained with cresyl violet.

The extent of the quinolinic acid lesions were examined microscopically. Subjects that were found to possess incomplete or misplaced lesions were excluded ($n=5$).

Statistical analysis. Differences in locomotor counts during the conditioning trials were evaluated using a three-way (group × lesion × trial) analysis of variance with repeated measures (Huynh-Feldt adjustment of degrees of freedom). Separate univariate analyses were also performed to evaluate potential group differences between and within lesioned and non-lesioned subjects. Reverse Helmert contrasts were performed to further assess potential group differences. The conditioned locomotion results were evaluated using a two-way analysis (group × lesion). Additional univariate analyses were performed on the lesioned and non-lesioned subjects to evaluate potential group differences. These analyses also included Reverse Helmert group contrasts to further assess these data. Post-hoc comparisons were made using Scheffe's procedure. Paired *t*-tests were used to assess the time spent in the drug paired environment before and after place preference conditioning. These within-subject comparisons are justified, given that the preconditioning values for the time spent on the non-start side did not differ between the two groups [$t(21)=0.99$, n.s.]. All statistical analyses were performed using SPSS: X version.3 software (SPSS: X User's Guide 1988).

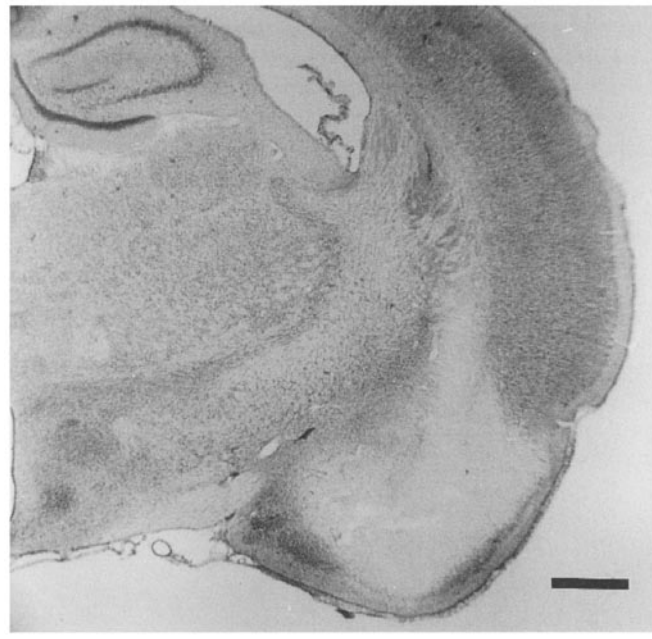

Fig. 1. Photomicrograph of the amygdaloid region of a representative subject following infusions of quinolinic acid. This 50 μm section is approximately 2.8 mm posterior to bregma, according to the atlas of Paxinos and Watson (1986). Scale bar = 1 mm

Results

Histology

Quinolinic acid lesions produced extensive damage to the amygdaloid complex (Fig. 1). A schematic representation of coronal sections from a representative lesioned subject is shown in Fig. 2. Only subjects that exhibited extensive bilateral amygdala lesions were included in this study. The most rostral portion of the lesion generally included the anterior amygdaloid area, with some subjects exhibiting damage to the substriatal region and the ventral endopiriform nucleus. Generally, the central, lateral, basolateral and basomedial nuclei were almost completely destroyed in all subjects. However, the medial and cortical nuclei were partially spared in some subjects. As a result of the magnitude of these lesions, most subjects exhibited a degree of extra-amygdalar damage. Due to their close proximity to the amygdala, the dorsal and ventral endopiriform nuclei were damaged in almost all rats. A small number of subjects exhibited damage to the ventral portion of the caudate putamen. Many lesioned subjects also displayed damage to the piriform cortex. No subject included in the study appeared to possess damage to the hippocampus.

In addition to the extensive gliosis produced by the quinolinic acid lesions, many subjects exhibited enlargement of the inferior horn of the lateral ventricle. This result appears to be due to the loss of tissue integrity as a consequence of neuronal destruction. In a preliminary

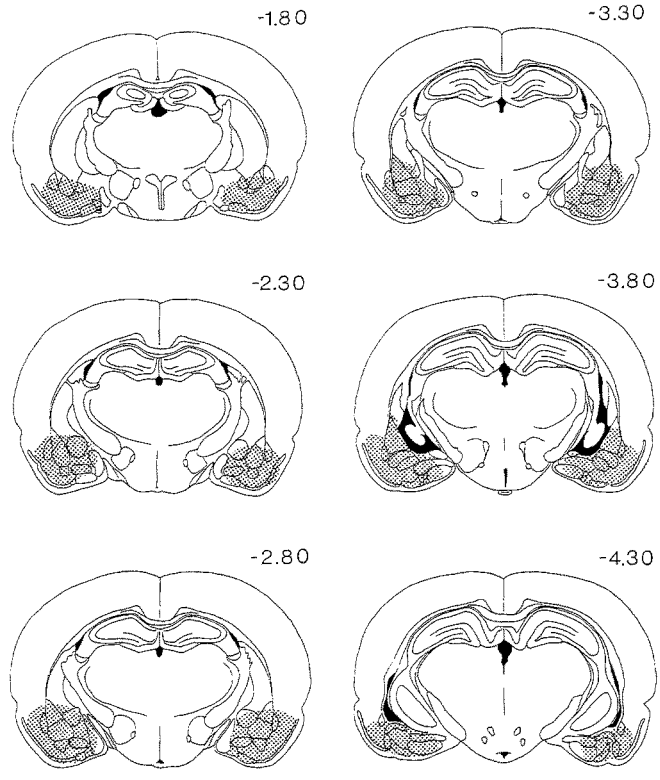

Fig. 2. Schematic of a representative bilateral lesion of the amygdala following infusions of quinolinic acid. The stipled area represents the area of neuronal loss. The values to the upper right of each coronal scetion indicate the anterior/posterior distance from bregma, according to the altas of Paxinos and Watson (1986)

study, these ventricular enlargements were not observed in lesioned subjects that were perfused 2–3 weeks after surgery. This finding suggests that the 2-month interval between surgery and histology may have contributed to this result. In agreement with other investigators (Jellestad and Cabrera 1986; Cahill and McGaugh 1990; Bermudez-Ratoni and McGaugh 1991), limited lesion-induced cavities were present in some subjects. This finding may also be a consequence of the long interval between surgery and histology, as subjects that were perfused 2–3 weeks after the infusion of quinolinic acid did not exhibit this histological feature. An additional factor worth noting is that quinolinic acid was prepared fresh before each infusion. Preliminary findings suggested that this procedure produced greater neurotoxicity than when toxin was prepared prior to surgery.

Conditioned locomotion

Amygdala lesions did not alter basal or cocaine-induced locomotion as no significant difference in locomotor counts was observed between lesioned and non-lesioned subjects for any of the experimental groups [$F(1, 60) = 0.09$, n.s.] (Fig. 3). Moreover, individual univariate analyses demonstrated that locomotor counts did not differ between lesioned and non-lesioned subjects that received saline, such as the control [$F(1, 21) = 0.75$, n.s.] or pseudoconditioned [$F(1, 19) = 0.00$, n.s.] groups, or the conditioned subjects that received cocaine [$F(1, 20) = 0.01$, n.s.]. However, a significant group effect was observed [$F(2, 60) = 90.34$, $P < 0.001$]. This group effect was due to the cocaine-induced locomotor counts of the conditioned subjects, as a Reverse Helmert analysis of this group effect revealed that there was no significant difference between the control and pseudoconditioned groups [$F(1, 60) = 0.01$, n.s.], although a highly significant difference between these control groups and the conditioned group [$F(1, 60) = 180.67$, $P < 0.001$] was present. A nonsignificant group × lesion interaction [$F(2, 60) = 0.03$, n.s.] further illustrates that the amygdala lesions failed to reliably alter locomotor activity. Although no significant effect of trials was observed [$F(6.78, 407.01) = 0.79$, n.s.], the group × trial interaction was significant [$F(13.57, 401.01) = 67.79$, $P < 0.001$]. Separate univariate analyses for each of the three groups demonstrated that this effect was due to a significant decrease in locomotor counts over trials for the control [$F(6.37, 133.79) = 17.48$, $P < 0.001$] and pseudoconditioned [$F(8.73, 165.91) = 20.63$, $P < 0.001$] groups. The conditioned subjects just failed to exhibit a significant increase in locomotor counts over trials [$F(8.06, 161.18) = 1.92$, $P < 0.06$].

The conditioning procedure produced a notable conditional behavioral effect, as indicated by a significant group effect [$F(2, 60) = 20.87$, $P < 0.001$] (Fig. 4). A Reverse Helmert contrast further indicated that there was no significant difference between the control and pseudoconditioned groups [$F(1, 60) = 0.46$, n.s.], but that the conditioned groups had significantly greater locomotor counts than other groups [$F(1, 60) = 41.29$, $P < 0.001$]. This behavioral effect was not affected by amygdala lesions as there was no significant effect of lesion [$F(1, 60) = 0.12$, n.s.] or group × lesion interaction [$F(2, 60) = 0.60$, n.s.]. Individual analyses demonstrated that amygdala lesions did not affect locomotor counts for control [$F(1, 21) = 2.19$, n.s.], pseudoconditioned [$F(1, 19) = 0.02$, n.s.] or conditioned [$F(1, 20) = 0.07$, n.s.] subjects. Moreover, separate univariate analyses demonstrated that significant group effects were apparent for both non-lesioned [$F(2, 27) = 17.71$, $P < 0.001$] and lesioned [$F(2, 33) = 7.162$, $P < 0.005$] subjects. In addition, Reverse Helmert contrasts demonstrate that control and pseudoconditioned groups do not differ significantly from each other for ei-

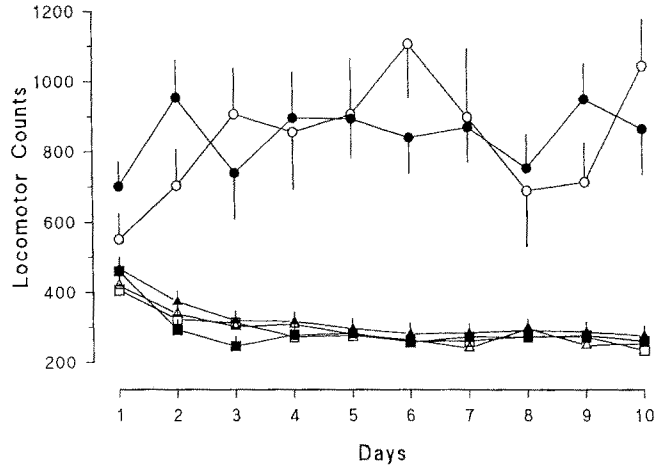

Fig. 3. Total locomotor counts during the 10 days of locomotor conditioning for nonlesioned control (△, $n = 10$), pseudoconditioned (□, $n = 10$) and conditioned (○, $n = 10$) subjects, as well as lesioned control (▲, $n = 13$), pseudoconditioned (■, $n = 11$) and conditioned (●, $n = 12$) subjects, Conditioned subjects received cocaine (10 mg/kg, i.p.) prior to being placed in the locomotor apparatus, while pseudoconditioned and control subjects were injected with saline. Values represent the group mean ± SEM

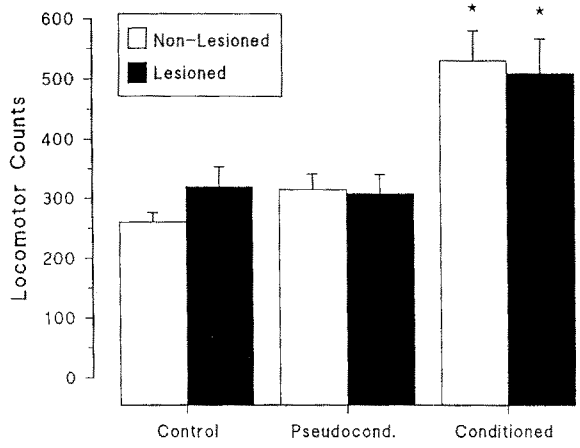

Fig. 4. Total locomotor counts for non-lesioned (□) control ($n = 10$), pseudoconditioned ($n = 10$) and conditioned ($n = 10$) subjects, as well as lesioned (■) control ($n = 13$), pseudoconditioned ($n = 11$) and conditioned ($n = 12$) subjects following 10 days of conditioning with cocaine (10 mg/kg, i.p.). Testing occurred 48 h after the last training session, and was conducted in the same apparatus as used for the training procedure. Values represent the group mean + SEM. * $P < 0.05$ compared to control or pseudoconditioned subjects

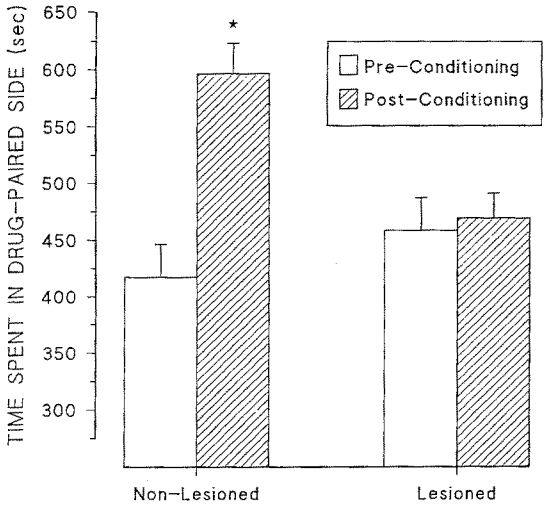

Fig. 5. Effect of cocaine (10 mg/kg, i.p.) on the time spent in the drug-paired (nonstart) compartment before (□) and after (▨) conditioning for non-lesioned ($n=10$) and lesioned ($n=13$) subjects. Values represent the group mean + SEM. * Indicates a significant within-group difference ($P<0.05$) of pre- vs. postconditioning scores

ther non-lesioned [$F(1, 27)=1.27$, n.s.] or lesioned [$F(1, 33)=0.04$, n.s.] subjects, while conditioned subjects exhibited significantly more locomotor counts than these controls for both non-lesioned [$F(1, 27)=34.15$, $P < 0.001$] and lesioned [$F(1, 33)=14.33$, $P < 0.001$] subjects. Post-hoc comparisons revealed that both non-lesioned and lesioned conditioned subjects exhibited significantly more locomotor counts than either control or pseudo-conditioned subjects ($P < 0.05$; Fig. 4).

Conditioned place preference

Non-lesioned subjects exhibited a robust cocaine-induced CPP, as illustrated by a significant increase in the time spent on the drug-paired side of the apparatus [$t(9)=6.20$, $P < 0.001$] (Fig. 5). In contrast, lesioned subjects did not exhibit an increase in time spent on the drug-paired side of the apparatus [$t(12)=0.33$, n.s.] (Fig. 5), suggesting that cocaine-induced CPP was blocked by the amygdala lesions.

Discussion

In agreement with previous reports (Post et al. 1988; Cador et al. 1989), excitotoxic lesions of the amygdala did not affect basal or cocaine-induced locomotor activity. This finding indicates that the amygdaloid complex is not a substrate for the unconditioned psychomotor stimulant effects of cocaine. Lesions of the amygdaloid complex also failed to affect cocaine-induced conditional locomotion, a somewhat unexpected result given previous data implicating these nuclei in this form of classical conditioning (Post et al. 1988; Brown et al. 1992). Despite an absence of effect of these excitotoxic lesions on the unconditioned locomotor effects of cocaine, as well as cocaine-induced conditional locomotor activity, destruction of the amygdaloid complex blocked cocaine-induced CPP.

Conditioned locomotion

The failure of amygdala lesions to alter cocaine-induced conditional locomotion was unanticipated given that electrolytic and 6-hydroxydopamine lesions of the amygdala have been reported to greatly attenuate environment-specific cocaine-sensitization (Post et al. 1988) and that exposure to a cocaine-paired environment produces an increase in c-fos expression in the amygdala (Brown et al. 1992). Moreover, a large body of evidence strongly implicates various nuclei of the amygdala in stimulus-reinforcement learning (Weiskrantz 1956; Jones and Mishkin 1972; Mishkin and Aggleton 1981; Gaffan and Harrison 1987; Cador et al. 1989; Everitt et al. 1991; Hiroi and White 1991; Kentridge et al. 1991). The second experiment demonstrated that cocaine-induced CPP was blocked by excitotoxic lesions of the amygdala, indicating that destruction of the amygdala can affect certain forms of cocaine-induced conditioning.

One explanation for the failure of amygdala lesions to affect cocaine-induced conditional locomotion relates to the learning demands of this paradigm. Although lesions of the amygdaloid complex clearly can produce impairments in learning of stimulus-reward associations (Weiskrantz 1956; Jones and Mishkin 1972; Gaffan and Harrison 1987; Cador et al. 1989; Kesner et al. 1989; Cahill and McGaugh 1990; Kentridge et al. 1991), the deficits are evident only in certain situations. For example, both Weiskrantz (1956) and Jones and Mishkin (1972) have noted that amygdala lesions do not completely or irreversibly block the learning of all stimulus-reward associations. Specifically, Jones and Mishkin (1972) suggest that "... only when associative learning demands are high, as in discrimination reversal, for example, will the animal show a severe and prolonged impairment." There is considerable experimental support for this proposal as many investigators have reported that amygdala lesions fail to produce substantial deficits in certain tasks that are based on the formation of stimulus-reward associations (Schwartzbaum 1965; Pellegrino 1968; Shuckman et al. 1969; Slotnick 1985; Cahill and McGaugh 1990; Kentridge et al. 1991). It is noteworthy that the conditioned locomotion procedure utilized in the present study involved multiple cocaine-environment pairings, and required a rudimentary discrimination involving multimodal stimuli (homecage versus testcage), and a contextual conditioned stimulus for cocaine administration. Although no single critical factor appears to predict if amygdala lesions will produce deficits in learning, the design of the present conditioned locomotion experiment was not biased in favor of observing a lesion effect, given the long postoperative recovery period before conditioning, the simplicity of the task and the number of conditioning trials. Similar factors may also contribute to the discrepancy between the present findings and those of Post et al. (1988), who reported that amygdala lesions

attenuate environment-specific cocaine sensitization. These investigators used a one-trial learning paradigm, which may have biased their result in favor of observing a lesion effect. It is also important to note that this interpretation of the present results does not preclude the possibility that the amygdala is involved in this form of conditioning in non-lesioned subjects, given that recovery of function via other structures and pathways is possible (Jones and Mishkin 1972).

Conditioned place preference

Although lesions of the amygdaloid complex failed to attenuate cocaine-induced conditional locomotion, the destruction of this region blocked cocaine-induced CPP. This result is in agreement with previous reports that destruction of specific amygdaloid nuclei attenuate amphetamine- (Hiroi and White 1991) and food- (Everitt et al. 1991) induced CPP. Although the findings of Hiroi and White (1991) and Everitt et al. (1991) implicate different amygdaloid nuclei as being critically involved in CPP, the extensive connectivities between amygdaloid nuclei (Krettek and Price 1978; Nitecka et al. 1981; Ottersen 1982; Aggleton 1985; Smith and Millhouse 1985) suggest that several nuclei may be involved in stimulus-reward learning. For example, in addition to the well documented role of the central nucleus in conditioned fear (Applegate et al. 1982; Pascoe and Kapp 1985; Hitchcock and Davis 1986, 1987; Davis 1992), it has recently been demonstrated that the lateral and/or basolateral nuclei of the amygdala play a role in fear-potentiated startle (Sananes and Davis 1992). The importance of a given nucleus in stimulus-reward associations may depend on the modality of the incoming sensory information, the specific demands of the associations and the characteristics of the response. Although the present findings demonstrate that lesions of the amygdala abolish cocaine-induced CPP, it cannot be determined if this effect is due to the blockade of the acquisition or expression of conditioning. Hiroi and White (1991) have obtained data that are consistent with a role for the amygdala in the expression of amphetamine-induced CPP, as well as a potential role in the acquisition of conditioning. This is consistent with other data showing a role of the amygdala in both the acquisition and expression of stimulus-reward associations (Jones and Mishkin 1972; Mishkin and Aggleton 1981; Murray 1991; Davis 1992; Helmstetter 1992). The present CPP data support the proposal that nuclei within the amygdaloid complex can play an essential role in the association of environmental stimuli with reward.

The role of the amygdala in cocaine-induced conditioning

Although both cocaine-induced conditional locomotion and CPP involve the formation and expression of stimulus-reward associations, only cocaine-induced CPP was affected by amygdala lesions. This differential effect may reflect the distinct learning demands of the two paradigms. For example, subjects in the CPP experiment were required to discriminate between two highly similar environments, while subjects in the conditioned locomotion experiment were only required to discriminate a novel environment from their homecage. However, these results may also reflect the fact that stimulant-induced conditional locomotion and CPP are behaviorally distinct phenomena, and hence could be subserved by different neural circuits. Stimulant-induced conditional locomotion is clearly a form of classical conditioning, with the conditioned response resembling the unconditioned response. The conditioned response of CPP, however, appears to be a form of approach/orienting behavior and does not resemble the unconditioned response to cocaine; hence it cannot be explained in terms of traditional Pavlovian conditioning (Wise 1989). It is noteworthy that a recent study has demonstrated that lesions of the central nucleus of the amygdala can differentially affect different classes of appetitively conditioned behaviors (Gallagher et al. 1990). Specifically, destruction of the central nucleus impaired the acquisition of conditioned orienting responses, but produced no deficit in the conditioning of behaviors originally evoked by the unconditioned stimulus. The differential effect of amygdala lesions on conditional locomotion and CPP is remarkably similar to these findings, and may provide support for the proposal that the acquisition of these two classes of appetitively conditioned responses are subserved by distinct neural mechanisms (Holland 1984). Taken as a whole, the data from these experiments support the proposal that nuclei within the amygdaloid complex can play a role in the association of environmental stimuli with reward. However, the importance of this structure appears to be dependent on the demands of the learning paradigm and/or the responses examined.

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