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# The Effects of Thalamic Paraventricular Nucleus Lesions on Cocaine-Induced Locomotor Activity and Sensitization

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YOUNG, C. D. AND A. Y. DEUTCH. *The effects of thalamic paraventricular nucleus lesions on cocaine-induced locomotor activity and sensitization*. PHARMACOL BIOCHEM BEHAV **60**(3) 753–758, 1998.—The brain circuitry that subserves the augmented locomotor response to repeated psychostimulant administration has been the subject of intense scrutiny. The dopaminergic innervation of the nucleus accumbens is critically involved in psychostimulant-elicited behavioral sensitization, and recent studies suggest that lesions of structures that send glutamatergic projections to the nucleus accumbens alter the acquisition or expression of psychostimulant-elicited sensitization. Although certain thalamic nuclei provide a major glutamatergic input to the striatum, the involvement of the thalamus in psychostimulant-elicited sensitization has not been investigated. We therefore examined the effects of lesions of the thalamic paraventricular nucleus, which projects to the shell of the nucleus accumbens, on cocaine-elicited locomotor sensitization. Lesions of the paraventricular nucleus did not alter basal locomotor activity, but significantly enhanced the acute locomotor response to cocaine. In contrast, repeated cocaine administration did not progressively augment locomotor activity in lesioned rats, but did so in sham-lesioned animals. The thalamic lesions also blocked the conditioned locomotor response to the environment in which the cocaine injections took place. These data suggest that the thalamic paraventricular nucleus may be an integral part of extended circuitry that subserves both the conditioned and nonconditioned components of psychostimulant-induced behavioral sensitization. © 1998 Elsevier Science Inc.

Cocaine Dopamine Nucleus accumbens Sensitization Thalamic paraventricular nucleus

RATS repeatedly administered cocaine or other psychostimulants develop an enhanced locomotor response to these drugs (26,41,43). This behavioral sensitization appears to involve both specific sensitization and contextual (environmental) conditioning. Thus, animals receiving intermittent administration of cocaine will respond to subsequent cocaine challenges with an enhanced locomotor response, and sensitized rats that are exposed to the environment in which psychostimulant injections were made will also exhibit a significant increase in locomotion (2,3,5,17,39,45,46).

The neural substrates of stimulant-induced behavioral sensitization are thought to involve central dopamine (DA) systems [see (26)]. The mesolimbic DA system, particularly the projection from the DA neurons in the ventral tegmental area (VTA) to nucleus accumbens (NAS), appears to be critical for both the acquisition and expression of behavioral sensitization. Accordingly, there has been considerable interest in the regulation of mesoaccumbal DA neurons by specific afferents. Recently, attention has focused on the role of glutamate–dopamine interactions in the development and expression of sensitization (24,25,27,28,32,44,45,52).

Lesions that disrupt certain glutamatergic projections to the NAS, including those from the prefrontal cortex, hippocampus, and amygdala, alter the locomotor response to acute psychostimulant challenge (11,22,33). Recent reports have suggested that such lesions also interfere with psychostimulant-elicited behavioral sensitization. Lesions of the medial prefrontal cortex, amygdala, and fornix (disrupting hippocampal projections to the NAS) have all been reported to modify the acquisition or expression of sensitization (40,53–55), although there is some disagreement concerning the effects of fornix/fimbria lesions (9,53–55).

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A major source of glutamatergic striatal afferents that has not been examined in the context of psychostimulant-elicited sensitization is the thalamus. The midline/intralaminar thalamic nuclei project to the striatal complex (4,6,8,21,29,47). In particular, the thalamic paraventricular nucleus (PV) projects to the NAS and other limbic sites, including the PFC, amygdala, and hippocampus (6,21,34,47,49); these projections are predominantly glutamatergic (14,18,42). The PV also receives a dopaminergic innervation, in part derived from the VTA (20,35,36,48), and PV neurons express $D_3$ (but not $D_1$, $D_2$, $D_4$, or $D_5$) mRNA (31). The anatomical relationships between the PV and its forebrain projection fields position the PV to influence activity in extended circuits that subserve psychostimulant actions.

In a study examining the metabolic activation of neurons in response to the unconditioned and conditioned effects of cocaine, Brown et al. (10) found that the conditioned locomotor response to cocaine administration involves a limited number of sites, including the PV. We have recently observed that several psychostimulants, including cocaine, induce the expression of the immediate-early gene c-*fos* in the PV but not the laterally contiguous mediodorsal thalamic nucleus (19). Because pretreatment with the $D_{2/3}$ DA receptor antagonist raclopride blocks cocaine-induced Fos expression (19), and PV neurons express only the $D_3$ receptor transcript (31), psychostimulant-elicited Fos induction in the PV appears to involve dopamine $D_3$ receptors. Together, these data suggest that the thalamic paraventricular nucleus may subserve certain actions of psychostimulants. We therefore examined the effects of PV lesions on cocaine-induced locomotor activity and sensitization.

## METHOD

### *Subjects*

Adult male Sprague–Dawley rats (CAMM, Wayne, NJ) were group housed under temperature- and humidity-controlled conditions on a 12 L:12 D schedule (lights on at 07 00 h). Food and water were available *ad lib*. The studies reported were carried out in accordance with the *Guide for the Care and Use of Laboratory Animals* as adopted and promulgated by the National Institute of Health.

### *Surgery*

Rats were randomly assigned to undergo either electrolytic lesions of the PV ($n = 16$) or sham lesions ($n = 12$). Rats were deeply anesthetized with chloral hydrate/pentobarbital. Lesions were accomplished by inserting stainless steel electrodes (0.4 mm OD), insulated except for terminal 0.5 mm, into four different sites along the anteroposterior extent of the PV [AP: −1.8/−2.5/−3.2/−3.8, DV −5.8/−5.8/−5.8/−5.9, L 0/0/0/0/0, according to the atlas of Paxinos and Watson (38)]. Constant anodal current (0.25 mA) was applied at each of the four sites for 12 s. For the sham lesions, the procedure was identical except that no current was passed through the electrode. Animals were allowed to recover for 21 days prior to behavioral testing.

### *Behavioral Testing*

All testing was conducted in a room located near the home colony room. The testing room had a masking noise present and was illuminated by red light; testing was conducted between 10 00 and 16 00 h. A shelving unit held eight photocell activity chambers (Omnitech, Columbus, OH), which allowed eight individual rats to be tested simultaneously. The activity chambers had eight pairs of photobeams positioned along the long axis of the cage, at a height of 1 inch above the floor. Locomotor activity (ambulation), counting interruptions of alternate beams, was recorded over 10-min periods. Between each testing session, the chambers were wiped clean with a 20% ethanol solution, and a thin layer of clean corncob bedding was sprinkled on the floor of each bin.

Half of the lesioned rats and half of the sham rats were randomly assigned to receive either cocaine or vehicle injections. On postoperative day 22, all animals were exposed to the locomotor apparatus for an acclimatization period of 60 min. On each of the succeeding 5 days (designated days 1–5), rats were placed in the chambers and allowed 30 min to acclimate; the animals were then injected with either cocaine hydrochloride (15 mg/kg, IP) or vehicle, and locomotor activity was monitored for 60 min.

Ten days after the last (day 5) cocaine or vehicle injection, rats were challenged with either cocaine (15 mg/kg, IP) or vehicle; 2 days later they were rechallenged with cocaine or vehicle in a counterbalanced manner (i.e., with the opposite treatment to that administered 2 days previously).

### *Lesion Analysis*

Animals were sacrificed and the brain postfixed and cryoprotected. Frozen coronal sections (40 μm) were cut from the decussation of the anterior commissure to the mesencephalon. The sections were mounted and stained with cresyl violet. Lesion extents were then reconstructed and charted.

### *Statistical Analyses*

Activity levels (photobeam interruptions) were analyzed by one-way repeated measure ANOVAs, using a within-subject design across days. All between-group data were also analyzed with one-way ANOVAs. When indicated, post hoc analyses were conducted using Newman–Keuls pairwise sequential method.

## RESULTS

### *Baseline Ambulation*

PV lesions did not alter baseline locomotor activity relative to sham-lesioned rats, nor did activity levels in vehicle-injected lesioned rats differ from those seen in vehicle-injected sham-lesioned rats on any of the test days (Fig. 1).

### *Cocaine-Elicited Locomotor Activity*

PV-lesioned rats showed a significantly greater increase in activity on the first day of cocaine administration than did sham-lesioned rats administered cocaine, $F(1, 13) = 8.07$, $p = 0.01$ (see Fig. 1). However, cocaine-elicited activity levels in the PV-lesioned rats did not differ from those in sham-lesioned rats treated with cocaine on any of the subsequent four days (Fig. 1). When PV-lesioned rats were given vehicle injections for the first 5 days and challenged with cocaine 10 days later (day 15), these animals also displayed a significant locomotor activity increase compared to corresponding sham-lesioned rats (Fig. 2 ). These data thus confirm the observation that acute cocaine administration to naive rats with PV lesions results in a heightened locomotor response to the psychostimulant.

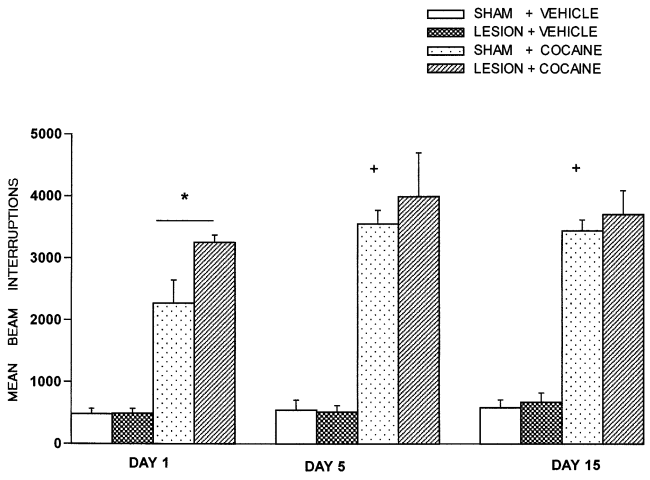


FIG. 1. Locomotor activity in response to cocaine administration. On the first day of cocaine administration, PV-lesioned animals showed a significant enhancement of the locomotor response compared to sham-lesioned animals. Sham-lesioned rats demonstrated a significant further increase in cocaine-elicited activity on days 5 and 15, but PV-lesioned animals did not show a sensitized locomotor response. $^{*}p \leq 0.01$; $^{+}p \leq 0.05$.

*Cocaine-Elicited Locomotor Sensitization*

Sham-lesioned rats that received daily cocaine sensitized to the locomotor effects of the drug, $F(4, 29) = 4.86, p = 0.007$ (see Fig. 1). Thus, the activity levels on day 5 were significantly higher than those recorded on day 1 (Fig. 1). Moreover, sham-lesioned rats that received daily cocaine still showed a sensitized locomotor response when challenged on day 15, i.e., 10 days after the last cocaine injection, $F(5, 11) = 14.1$, $p = 0.010$; see Fig. 1). In contrast, PV-lesioned rats did not significantly sensitize across the first 5 days of drug administration, $F(7, 39) = 1.03$, $p = 0.41$), or exhibit a sensitized response after a 10-day holiday from drug injections, $F(7, 15) = 1.24$, $p = 0.30$; see Fig. 1).

*Cocaine-Associated Locomotor Conditioning*

Sham-lesioned rats that received daily cocaine demonstrated pairing of environmental cues with the cocaine injections. Thus, administration of vehicle 10 days after the cocaine injections resulted in a significant increase in activity compared to rats that received vehicle for the first 5 days, $F(1, 11) = 6.93$, $p = 0.03$ (see Fig. 3). In contrast, PV-lesioned rats did not exhibit significant contextual conditioning, $F(1, 15) = 2.75$, $p = 0.12$ (Fig. 3).

*Lesion Extent*

Cresyl violet-stained sections revealed discrete lesions of most of the PV that infringed minimally on the laterally contiguous mediodorsal thalamic nucleus, and did not involve the dorsolaterally adjacent medial habenula or fasciculus retroflexus (see Fig. 4). In many animals the lesions extended ventrally to encroach upon the intermediodorsal thalamic nucleus; the central medial nucleus was not involved. The PV lesions typically spared the most anterior aspects of the PV (rostral to the anterior pole of the anteromedial nucleus) and only partially involved the most caudal PV.

## DISCUSSION

Baseline locomotor activity was not affected by lesions of the PV, but PV-lesioned rats were significantly more responsive to acute cocaine administration. Despite the greater sensitivity to cocaine on day 1, activity levels in PV-lesioned rats did not progressively augment with daily cocaine injections.

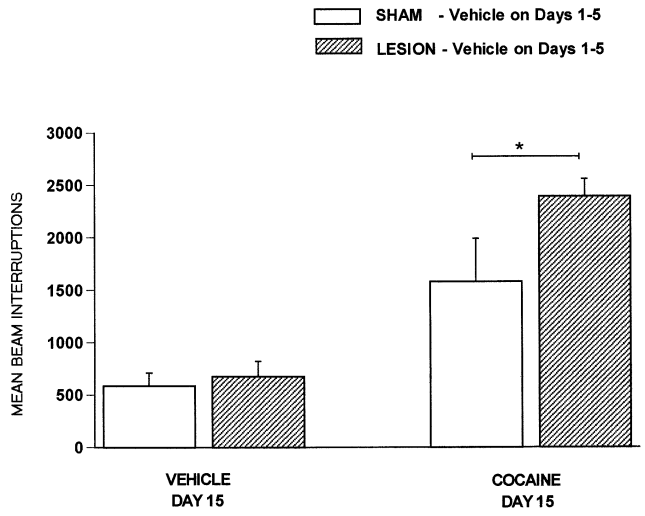


FIG. 2. PV-lesioned rats that received vehicle on days 1–5 and then cocaine on challenge day 15 showed a significant increase in locomotor activity compared to similarly treated sham-lesioned animals. The PV-lesioned animals therefore show a heightened response associated with the initial exposure to cocaine, confirming the observed augmentation of activity in lesioned animals also exposed to cocaine for the first time on day 1. $^{*}p \leq 0.05$.

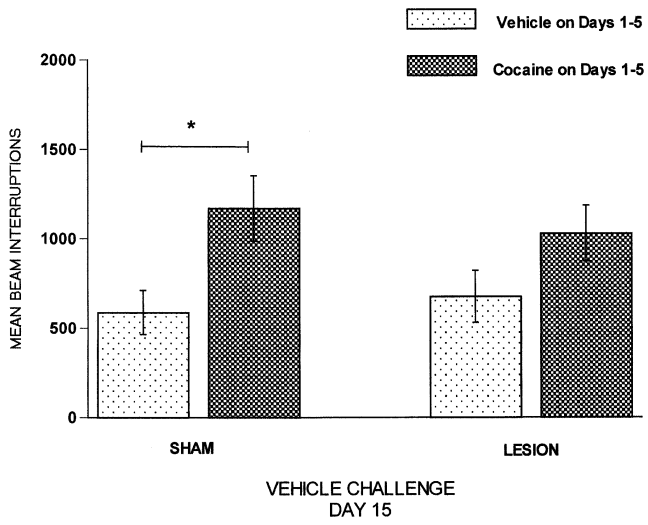


FIG. 3. Contextual conditioning in response to chronic cocaine administration. Sham-lesioned rats that received cocaine on days 1–5 showed a significant locomotor response when administered vehicle on challenge day 15, indicating a conditioned response to the psychostimulant-associated activity chamber. However, PV-lesioned rats did not demonstrate a significant increase in locomotor activity when exposed to the psychostimulant-paired chamber, indicating a disruption of the conditioned locomotor response to cocaine ($p \leq 0.05$).

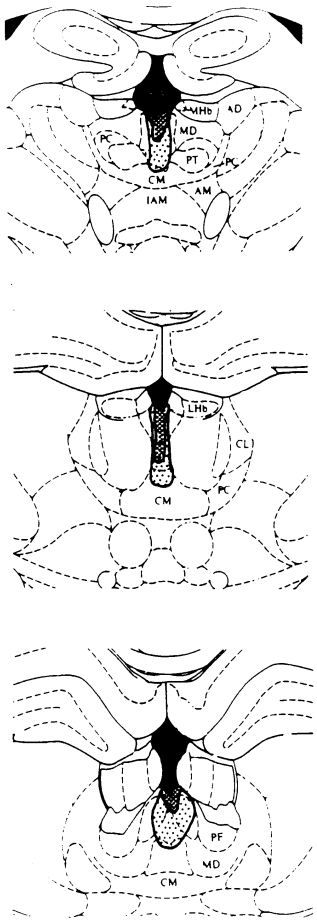


FIG. 4. Reconstruction of PV lesion extents, depicting the smallest (dense stipple) and the largest (light stipple) lesion. The lesions are charted on figures adapted from Paxinos and Watson (38).

Similarly, PV-lesioned rats did not exhibit significant contextual conditioning to the locomotor apparatus. These data suggest that the PV may be an important site in the extended circuitry subserving psychostimulant-elicited activity and behavioral sensitization.

The finding that PV lesions significantly enhanced the locomotor response to acute cocaine administration is similar to previous data from lesion studies of other glutamatergic afferents to the NAS. For example, lesions of the prefrontal cortex and hippocampus also enhance the locomotor response to acute psychostimulant challenge, yet do not alter baseline locomotor activity (11,22,23,33,40,51,53). Interestingly, both hippocampal and prefrontal cortical lesions also lead to increased DA utilization or release in the NAS under challenge (e.g., psychostimulant administration) but not basal conditions (15,33).

An increase in cocaine-elicited locomotion in PV-lesioned rats relative to sham-lesioned controls was observed on the first day of cocaine injection. We did not observe any subsequent sensitization of the locomotor response. This may be due to the already elevated response to acute cocaine injection on day 1 and a resultant ceiling effect. However, the observation that the PV lesion blocked the conditioned locomotor response to cocaine cannot be due to a ceiling effect, because the PV-lesioned rats show much greater activity levels in response to cocaine than environmental cues. The ability of PV lesions to block the conditioned locomotor response to cocaine corresponds well with a study by Brown et al. (10) in which cocaine-elicited expression of the immediate-early gene c-*fos* was monitored. Brown and colleagues reported that acute cocaine administration increased the number of Fos-like immunoreactive cells in both the PV and NAS, but in animals exposed to the environment in which the cocaine injections were made only PV neurons showed the increase in Fos-li neurons. These data also fit well with reports that suggest that lesions of glutamatergic afferents to the NAS from the PFC or basolateral amygdala block the conditioned locomotor response to psychostimulants (39,40), although this conclusion concerning amygdala lesions has recently been challenged (1). Because the noncompetitive NMDA receptor antagonist MK-801 blocks the conditioned locomotor response to cocaine and amphetamine (16,45), it appears likely that glutamatergic projections are specifically involved. It is possible that specific behavioral sensitization to psychostimulants and the conditioned locomotor response (contextual conditioning) to psychostimulants may be dissociated, involving two (or more) different sites of action [see (45)].

The mechanisms through which the PV may regulate locomotor responses to psychostimulants are not clear. The PV receives a dopaminergic innervation (19), which originates in part from the VTA (35,36,48), and the $D_3$ DA receptor transcript (but not other DA receptor mRNAs) is expressed in PV neurons (31). Thus, it is possible that cocaine is acting directly in the PV to increase extracellular DA levels and thereby influence PV neurons that express the $D_3$ receptor and project to the nucleus accumbens. This idea is particularly intriguing in light of the suggestion that cocaine reinforcement depends upon $D_3$ receptors in the nucleus accumbens (13,37). However, given the use of electrolytic lesions in this study, we cannot eliminate the contribution of disruption of fibers of passage, or retrograde degeneration of cells located in afferent sources secondary to pruning of the terminals of these projections in the PV.

The PV also receives relatively dense serotonergic, noradrenergic, and adrenergic innervations (7,12,30,35), and appropriate receptors for these transmitters are present in the PV. Because cocaine increases extracellular levels of these amines as well as DA, these other transmitters may be involved in the actions of cocaine in the PV. However, we have reported that cocaine-elicited Fos induction in the PV is completely blocked by pretreatment with the $D_{2/3}$ DA antagonists raclopride and sulpiride (19), suggesting that the actions of DA are critical.

The PV may be part of an extended neural system that subserves different aspects of the behavioral responses to psychostimulants. We observed that the locomotor response to initial cocaine administration is enhanced but the conditioned response to cocaine is disrupted by lesions of the PV. These data suggest that the medial thalamus plays an important role in the intense conditioned response exhibited by cocaine abusers to the milieu in which the drug is ingested. Recent in vivo imaging data suggest that the medial thalamus is involved in cocaine craving (50), which is strongly cued by environmental stimuli. Further studies of the thalamic paraventricular nucleus are warranted, and may offer insights into the development of effective treatments for cocaine abuse.

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