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ORIGINAL INVESTIGATION

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Repeated exposure to inhaled toluene induces behavioral and neurochemical cross-sensitization to cocaine in rats

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Abstract *Rationale*: Toluene is a solvent found in many commercial products and is frequently abused by inhalation. Whether previous exposure to toluene alters subsequent responses to other drugs of abuse is not known. *Objectives*: This study determined the effects of repeated toluene exposure on the acute motor-stimulant response to cocaine and on cocaine-induced dopamine (DA) concentrations in the nucleus accumbens (NAc). *Methods*: One week following bilateral cannulae implantation over the NAc, 27 adult, male Wistar rats began a daily 30-min exposure regimen to either toluene (8000 ppm) or air for ten sessions. Approximately 24 h or 96 h after their last exposure, animals were injected with either saline or cocaine (15 mg/kg, i.p.) and locomotor activity and DA concentrations in the NAc were measured. *Results*: Exposure to toluene rendered the rats immobile, and the time required for recovery of normal posture decreased across the ten sessions. In all animals tested, systemic cocaine administration enhanced both locomotor activity and DA concentrations in the NAc. These increases, however, were significantly greater in rats previously exposed to toluene. *Conclusions*: Overall, these findings show that repeated toluene exposure enhances behavioral and neurochemical responses to subsequent cocaine administration.

Keywords Cross-sensitization · Inhalants · Toluene · Cocaine · In vivo microdialysis · Locomotor activity

Introduction

The abuse of volatile inhalants such as toluene is a significant problem in both the United States and less-developed nations (Balster 1997). Inhalants are readily available in a variety of commercial products including, but not limited to, household and industrial-type cleaning fluids, adhesives, paints and many solvents for rubber, varnishes, oils and waxes. It is likely that the widespread and relatively inexpensive availability of inhalants contributes to their abuse among children and adolescents (Streicher et al. 1981; Flanagan and Ives 1994). In this regard, surveys of drug use estimated that, in 1997, approximately 21% of American 8th-graders experimented with inhalants, while 11.8% and 5.6% of those tested had used inhalants within the past year and month, respectively (US Department of Health and Human Services 1999).

Toluene is considered the prototypic abused solvent (Balster 1997). Among its behavioral effects, toluene can increase locomotor activity and schedule-controlled operant behavior at low to intermediate doses and decrease these behaviors at high doses (Moser and Balster 1981; Kjellstrand et al. 1985; Taylor and Evans 1985; Hinman 1987; Wood and Colotla 1990; Bowen and Balster 1998). Among its neuropharmacological effects, toluene has been shown to increase dopamine (DA) content (Rea et al. 1984; Stengard et al. 1994) and DA receptor binding in the rat neostriatum (von Euler et al. 1993; Hillefors-Berglund et al. 1995), as well as mimic response patterns in mesolimbic DA neuronal firing produced by other drugs of abuse (Riegel and French 1999).

To date, very little is known about the effects of toluene exposure on subsequent responses to other drugs of abuse. von Euler and colleagues (1991, 1993) found that repeated toluene exposure enhanced the motor-stimulant response to apomorphine in rats, indicating that such exposure can produce cross-sensitization with a direct DA agonist. However, whether toluene exposure influences the subsequent behavioral or neurochemical effects of other abused drugs is not known. Thus, the purpose of the present study was to examine the effects of toluene exposure on acute behavioral and neurochemical responses to cocaine. Information of this sort may further elucidate the neurobehavioral basis of inhalant abuse and its potential role in the subsequent abuse of other drugs.

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Materials and methods

Animals and surgery

Animal studies were approved by the Louisiana State University Health Sciences Center Animal Resources Advisory Committee and were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Twenty-seven adult, male Wistar rats (Harlan Sprague-Dawley, Indianapolis, Ind.) weighing 350–400 g at the time of surgery were used. Throughout the experiments, animals had free access to food and water and were individually housed in an AAALAC-accredited facility that was maintained on a 12-h/12-h light/dark cycle (lights on at 0700 hours).

Rats, anesthetized with Equithesin (3.3 ml/kg, i.p.), were placed in a Kopf stereotaxic instrument (Tujunga, Calif.). All animals were bilaterally implanted with stainless-steel, 20-gauge guide cannulae (15 mm) which were directed 3 mm above the nucleus accumbens (NAc) and secured to the skull with three stainless-steel screws and dental acrylic. The coordinates for these surgeries were A/P+9.1 mm, D/V+8.0 mm and M/L±1.4 mm from the midline (Pellegrino et al. 1979). Immediately following surgery, animals received 0.2 ml (i.m.) of Flo-Cillin, an antibiotic containing 300,000 U/ml of penicillin G benzathine and penicillin procaine.

Inhalation exposure to toluene

Following 1 week of post-operative recovery, animals were exposed to either toluene (8000 ppm; n=15) or air (n=12) for five consecutive daily sessions, were left untreated for 2 days and were then exposed to toluene or air for an additional five consecutive sessions. For each of the ten exposure sessions, rats were individually placed into a modified airtight, cylindrical exposure chamber (diameter 30.5 cm, height 30.5 cm and volume 25 l) as previously described (Glowa 1987). All inhalation chambers were cleaned prior to use. Standard curves for injected toluene were determined over a range of three injection volumes (1 ml=2689.723 ppm, 2 ml=7450.341 ppm, 3 ml=10799.69 ppm; r=0.995; r^2=0.99). These concentrations were similar to those previously reported using the same chamber (Glowa et al. 1986; Glowa and Dews 1987). In those studies, concentrations of toluene reached peak levels within 10 min and remained stable until the chamber was opened. For the toluene-treated animals in the present study, toluene (2.25 ml – Fisher Scientific, Fair Lawn, N.J.) was injected onto absorbent paper at the bottom of the chamber. Rats were exposed for 30 min and then removed from the inhalation chamber. Each toluene-treated rat was placed on its side in its home cage, and the time required to regain normal posture (all four paws on the cage floor) was recorded.

In vivo microdialysis and locomotor activity

Approximately 16 h before the microdialysis/behavioral experiments began, concentric-style dialysis probes (3-mm active membrane) were inserted into the guide cannulae. To allow free mobility, the dialysis probes were attached to both a liquid swivel and a counterbalance rod. The probes were connected to an infusion pump (Harvard Apparatus, Holliston, Mass.) that allowed continuous perfusion of dialysis buffer [KCl=2.7, NaCl=140, $CaCl_2$=1.2, $MgCl_2$=1.2, phosphate-buffered saline (PBS)=0.2 (all in mM), pH=7.4] at a rate of 2 µl/min. The next morning, probes were perfused with dialysis buffer for at least 1 h before the start of dialysis experiments, after which four 20-min dialysis samples were collected. Animals then received a peripheral injection of either saline (1.0 ml/kg, i.p.) or cocaine (15 mg/kg, i.p. – Sigma, St. Louis, Mo.), and dialysis samples were collected for the next 3 h in 20-min intervals. Dialysate was collected into 20 µl of mobile phase containing 1×10^{-7} M of the internal standard dihydroxybenzylamine (DHBA) and was either stored at –80°C or immediately injected onto a high-performance liquid chromatography (HPLC) column. Microdialysis experiments were conducted approximately 24 h (dialysis day 1) and 96 h (dialysis day 2) following the last toluene or air exposure. In all circumstances, each NAc was dialyzed one time, and systemic drugs (e.g., saline or cocaine) were administered to each animal once in a randomized fashion.

Locomotor activity was measured throughout the microdialysis experiments. Motor activity was observed before and after systemic saline or cocaine administration (e.g., in the same 20-min intervals as dialysate collection) using a Digiscan Micro-monitoring system (Omnitech Electronics, Columbus, Ohio) that was interfaced with a Macintosh Classic II computer. Each motor activity chamber (45×24×19 cm) was equipped with 16 evenly spaced light beams (4.5 cm above the floor of the box) and was placed in a sound-attenuating chamber that included a fan to mask extraneous noise and a 10-W light bulb for ambient illumination.

High-performance liquid chromatography

A Rainin pump (Woburn, Mass.) was used to advance the mobile phase [all in mM: NaH_2PO_4=75, EDTA (disodium ethylenediamine tetraacetate)=0.01, octanesulfonic acid=0.8 and 11% acetonitrile v/v, pH=3.4, with H_3PO_4] through an octadecasilane reversed-phase column (Rainin) at a rate of 1.0 ml/min. HPLC detection conditions were the same as previously reported (Steketee 1998; Beyer and Steketee 1999). Briefly, the electrochemical detection system consisted of three coulometric electrodes (preoxidation electrode=–0.175 V, oxidation electrode=0.15 V and preinjection port electrode=0.4 V). Dialysates, including the internal standard, were injected onto the column and compared with an external standard curve ranging from 10^{-14} mol to 10^{-11} mol. These HPLC conditions allowed for determination of DA concentrations in the NAc.

Histologies

All animals were euthanized via an overdose of sodium pentobarbital and were perfused by intracardiac infusion of PBS (0.2 mM) and 4% formaldehyde. Brains were rapidly removed and stored in 4% formaldehyde until time of sectioning on a vibratome (Technical Products International Inc., St. Louis, Mo.). Next, sections were mounted on gelatin-coated slides and stained with cresyl violet to allow visualization of cannulae placement.

Data analysis

The time required for recovery of normal posture after exposure to toluene was analyzed using a one-way, repeated-measures analysis of variance (ANOVA) and Dunnet's post-hoc analysis. For microdialysis studies, DA data were converted to percentage of baseline to correct for interassay variability. Time courses of both locomotor behavior and neurochemical data were analyzed using a two-way ANOVA with one repeated measure (time). Multiple comparisons were made using a modified least significant differences test (Milliken and Johnson 1984).

Results

Following toluene or air treatment and at the beginning of the microdialysis studies, animals did not significantly differ in their mean body weights (data not shown).

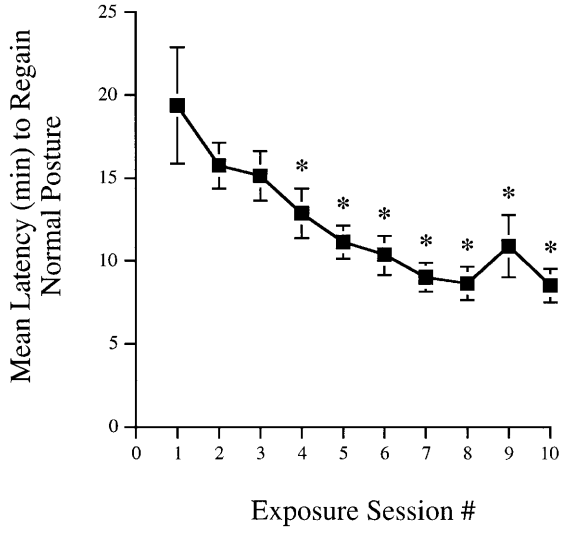

Fig. 1 Mean latency to regain normal posture (all four paws on the home-cage floor) after each consecutive toluene exposure. Each *point* indicates the mean for 12 rats. Data are expressed as the mean time (min) ±SEM required for recovery of normal posture. **P*<0.05 compared with first toluene exposure (session no.1)

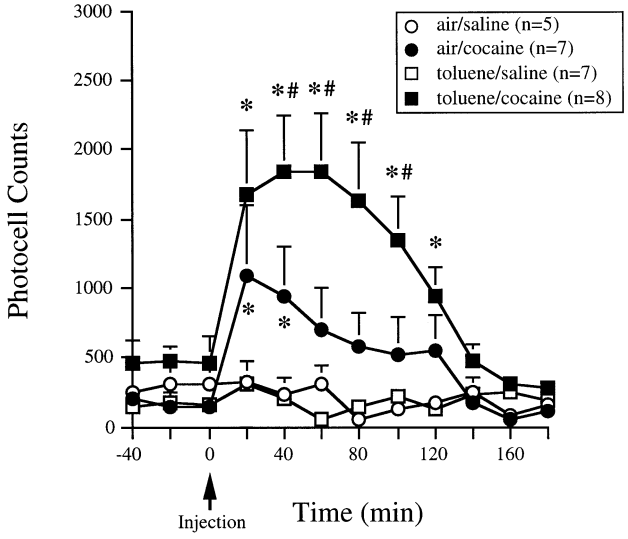

Fig. 2 Effects of toluene exposure on the acute motor-stimulant response to cocaine. Data represent mean photocell counts ±SEM at each 20-min time interval. The *arrow* indicates the time of peripheral injections. Significant differences between treatments were determined using repeated-measures analysis of variance followed by post-hoc testing using a modified least significant differences test (Milliken and Johnson 1984). **P*<0.05 comparing groups with air/saline and #*P*<0.05 compared with air/cocaine

Time required to regain normal posture following toluene exposure

Toluene exposure produced gross sedation in all rats. Upon removal from the inhalation chamber, mild body tremors, occasional jerking of the legs and nose twitching were observed in all toluene-exposed subjects. Figure 1 shows that the mean latency (±SEM) to regain normal posture following the first exposure to toluene was 19.1±3.2 min. Latencies gradually declined across exposures, resulting in a mean latency of 8.5±1.1 min after the last exposure. A repeated-measures ANOVA indicated a significant effect of exposure ($F_{9,11}$=6.510, P<0.001), and Dunnet post-hoc analysis indicated that righting latencies following exposures 4 through 10 were significantly lower (P<0.05) than the latency after the first exposure.

Effects of toluene on cocaine-induced locomotor activity

The effects of toluene treatment on the acute motor-stimulant response to cocaine (15 mg/kg, i.p.) are illustrated in Fig. 2. Basal (preinjection) locomotor activity varied across groups but did not differ significantly ($F_{3,23}$= 1.650, P=0.205) between treatment groups [air/saline, 340±118; air/cocaine, 184±100; toluene/saline, 153±100; toluene/cocaine, 419±93 (all in photocell counts ±SEM per 20-min interval)]. Systemic cocaine produced an increase in motor activity in both groups of animals for the initial 40 min of the experimental session. However, in rats repeatedly exposed to toluene, cocaine produced an increase in locomotor activity that was significantly greater than that of air-treated animals ($F_{3,23}$=6.066, P=0.003) and that was elevated longer following cocaine administration ($F_{12,276}$=8.373, P<0.001). A significant interaction effect was observed ($F_{36,276}$=3.909, P<0.001), and locomotor activity following saline injections was not different in animals previously exposed to either toluene or air.

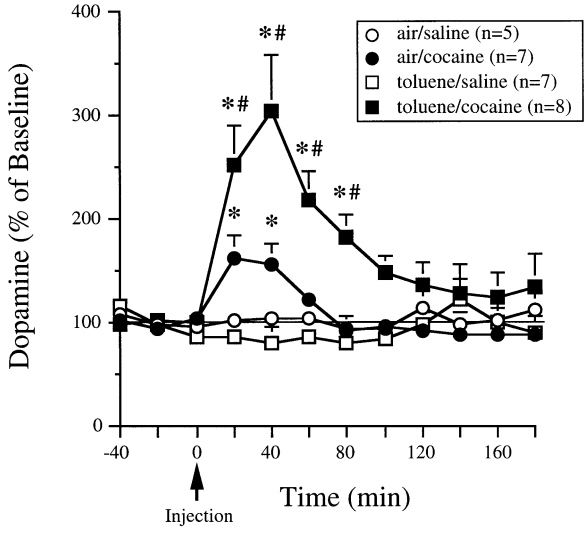

Fig. 3 Effects of toluene exposure on cocaine-induced extracellular dopamine (DA) concentrations in the nucleus accumbens (NAc). Neurochemical data are expressed as mean percentage of baseline ±SEM. Basal DA concentrations in the NAc were not significantly different between treatment groups. The *arrow* indicates the time of peripheral injections. The significance of the differences between treatments was determined using repeated-measures analysis of variance followed by post-hoc testing using a modified least significant differences test (Milliken and Johnson 1984). **P*<0.05 comparing groups with air/saline and #*P*<0.05 compared with air/cocaine

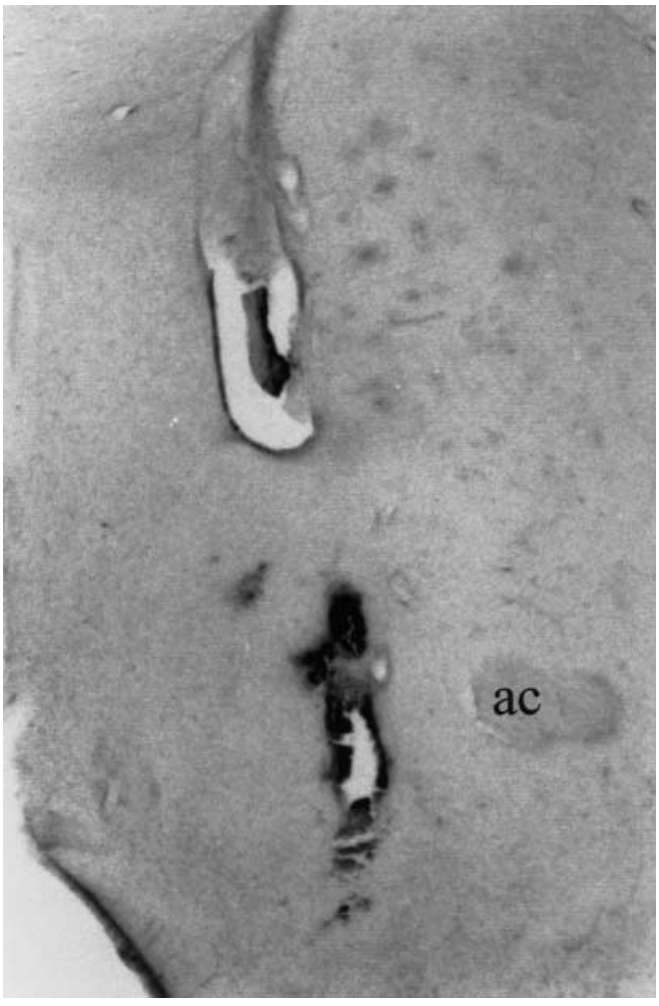

Fig. 4 Representative photomicrograph of guide cannulae and microdialysis probe placement in the nucleus accumbens (NAc). In all cases, the probe was located at or medial to the anterior commissure (ac) and greater than 60% of the active membrane was found in the boundaries of the NAc as described by the atlas of Paxinos and Watson (1986). Magnification=20× (Olympus scope with noncorrected lens)

Effects of toluene on cocaine-induced mesolimbic DA

Figure 3 illustrates the effects of toluene exposure on cocaine-induced DA concentrations in the NAc. No differences in basal dialysate levels were observed between experimental groups ($F_{3,23}$=0.604, P=0.619). The mean basal DA concentrations in the NAc were: air/saline, 11.1±3.5; air/cocaine, 12.0±2.8; toluene/saline, 22.0±14.0; toluene/cocaine, 9.5±1.5 (all in fmol/20-min sample). Cocaine produced an increase in extracellular DA concentrations in both groups of animals for the initial 40 min of the experimental session. However, in animals previously exposed to toluene, cocaine produced an increase in DA concentrations in the NAc that was significantly greater than that of air-treated animals ($F_{3,23}$=8.796, P<0.001) and that was elevated longer following cocaine administration ($F_{11,253}$=5.856, P<0.001). A significant interaction effect was observed ($F_{33,253}$= 4.371, P<0.001), and mesolimbic DA concentrations following saline injections were not found to be different in animals previously treated with either toluene or air.

Histology

Microdialysis probe placement in the rat NAc is shown in Fig. 4. In all circumstances, the active membrane of the probe was located within the boundaries of the NAc, as described by Paxinos and Watson (1986). On occasion, a small portion of the dialysis probe was found to be slightly dorsal or ventral to the NAc. However, cresyl violet-stained sections showed that greater than 60% of the active membrane was located at or medial to the anterior commissure (magnification ×20).

Discussion

Human abusers have been reported to consume toluene concentrations at approximately 10,000 ppm (Longley et al. 1967; Press and Done 1967). The present study indicates that repeated exposure to similar concentrations of toluene (8000 ppm) effects subsequent behavioral and neurochemical responses to acute cocaine (15 mg/kg, i.p.) in the rat. Specifically, systemic cocaine produced increases in locomotor activity and concentrations of DA in the NAc, but these effects were greater in rats previously exposed to inhaled toluene. These results are the first to demonstrate a cross-sensitization between toluene and cocaine and are consistent with the ability of toluene to enhance apomorphine-induced increases in locomotor activity (von Euler et al. 1991, 1993). Also, these results are consistent with previous findings that other drugs of abuse (e.g., amphetamine, morphine and caffeine) produce cross-sensitization with cocaine (Kazahaya et al. 1989; Lett 1989; Akimoto et al. 1990; Hirabayashi et al. 1991; Horger et al. 1991).

Previous work from numerous laboratories has demonstrated that toluene, like other central nervous system (CNS) depressants, produces a biphasic (e.g., inverted U-shaped) dose–effect curve on motor activity (Hinman 1987; Bowen and Balster 1998). At low concentrations (2000–3000 ppm), toluene increases spontaneous locomotor activity, while higher concentrations (10,000–15,000 ppm) decrease motor performance and ultimately produce severe ataxia and loss of the righting reflex (Kjellstrand et al. 1985; Hinman 1987; Wood and Colotla 1990). Accordingly, this study found that toluene exposure produced immobility and gross sedation in all animals. Tolerance developed to the motor-impairing effects of toluene, as indicated by the decrease in time required for animals to regain normal posture across sessions. Previous reports on the development of tolerance to toluene have provided equivocal results. For example, Hinman (1984) found that repeated toluene treatment

produced a shift to the right of the dose–effect curves for rearing and ataxia. However, tolerance did not develop to toluene-induced decreases in scheduled, controlled behavior (Moser and Balster 1981; Taylor and Evans 1985). These discrepancies may be due to differences in route of administration, length and dose of toluene exposure, species studied and the behavioral procedure employed (Evans and Balster 1991).

The mesolimbic DA pathway is activated by acute and repeated administration of most drugs of abuse (Koob 1992), and there is a strong correlation between enhanced DA concentrations and increased locomotor activity in rodent models of addiction (Wise and Bozarth 1987; Robinson and Berridge 1993). Toluene is readily abused by humans (Streicher et al. 1981; Flanagan and Ives 1994); however, the effects of toluene on DA concentrations in the NAc have not been reported. Nevertheless, evidence does exist supporting the notion that DAergic transmission is affected by toluene treatment. First, previous microdialysis studies have shown that acute toluene exposure increases DA concentrations in the striatum, a region receiving heavy mesolimbic DA input (Stengard et al. 1994). Second, electrophysiological studies demonstrate that inhaled toluene exposure initially stimulates and ultimately attenuates DA neuronal firing in the ventral tegmental area (Riegel and French 1999), an effect that is similar to other drugs of abuse (Gessa et al. 1985; DiChiara and Imperato 1988; French et al. 1997). Finally, subchronic and chronic exposure to low doses of toluene has been shown to affect DA utilization (Fuxe et al. 1982) and produce persistent changes in DA D_2 receptor binding in the rat neostriatal complex (von Euler et al. 1993; Hillefors-Berglund et al. 1995).

Other neurotransmitter systems may have contributed to the cross-sensitization between toluene and cocaine observed in the present study. Most notable are the glutamate and gamma-aminobutryic acid (GABA) systems. With regard to the former, Cruz and colleagues (1998) demonstrated that toluene abolishes, in a subunit-specific manner, glutamate (NMDA) receptor-stimulated currents in *Xenopus* oocytes. In the same study, toluene was not effective in altering other glutamate (kainate) receptor-induced currents. Additional studies from the same research group demonstrated that another abused solvent, 1,1,1-trichloroethane, also inhibits glutamate receptor (NMDA) function (Cruz et al. 1997). With regard to GABA, toluene treatment has been shown to alter extracellular concentrations of GABA in the cerebellum (Stengard et al. 1993), hippocampus (Ikeuchi et al. 1993) and globus pallidus (Stengard and O'Connor 1994) and produce discriminative stimulus effects that generalize to GABAergic agonists (Bowen et al. 1999). Taken together, these findings suggest the possible involvement of glutamatergic and GABAergic systems in mediating toluene-induced changes in the CNS. This relationship may be even more important given the purported ability of both glutamate and GABA to interact with DAergic systems (Johnson et al. 1992; Xi and Stein 1998).

In addition to exhibiting cross-sensitization with each other, most drugs of abuse demonstrate a cross-sensitization with stress. Acute and repeated exposure to various stressors (e.g., footshock and restraint stress) has been shown to effectively activate mesolimbic circuitry and psychostimulant-induced locomotor activity (Kalivas and Stewart 1991; Hamamura and Fibiger 1993; Sorg and Kalivas 1993). Stress has also been shown to affect glutamate systems (Fitzgerald et al. 1996). These findings suggest that stress, via interactions with DAergic and/or glutamatergic systems, may permissively mediate locomotor and neurochemical responses similar to those observed in the present study. This hypothesis is further supported by a recent study demonstrating that animals exposed to repeated formaldehyde inhalation develop behavioral cross-sensitization to cocaine (Sorg and Prasad 1997). Those authors speculate that because formaldehyde is not considered an abused substance, the cross-sensitized response was due to the stress associated with the formaldehyde exposure. A role for stress in the present study cannot be ruled out, as toluene exposure has been shown to increase plasma concentrations of norepinephrine (Hsieh et al. 1991), adrenocorticotropic hormone (Hsieh et al. 1991), glucocorticoids (Anderson et al. 1980) and corticosterone (Hsieh et al. 1991; Little et al. 1998). Collectively, these changes are indicative of hypothalamic–pituitary–adrenocortical (HPA) axis activation, the interface between the nervous, endocrine and immunological systems mediating the "stress response." In light of these findings, it is possible that the effects of toluene observed in the present study were due, in part, to stress-induced adaptations in the CNS. More research, however, is needed to appropriately study the interactions of stress and toluene.

In the present study, toluene-treated animals received cocaine on dialysis day 1, approximately 24 h after their last toluene exposure, or on dialysis day 2, approximately 96 h after their last toluene exposure. Interestingly, it was observed that cocaine elicited a greater motor-stimulant response in animals previously exposed to toluene when administered on dialysis day 2 than those animals receiving cocaine on dialysis day 1 (data not shown). This phenomenon was not observed when assessing the neurochemical data from the same animals (data not shown). The behavioral observation in the present study is consistent with studies showing that a challenge injection of cocaine produced a greater effect when administered 2 weeks (Kalivas and Duffy 1993) or 1 month (Henry and White 1995) rather than 24 h following cessation of repeated cocaine treatment. Thus, it is possible that behavioral cross-sensitization between toluene and cocaine may have been more pronounced if measured at greater time intervals following the last exposure to toluene. However, further studies investigating this temporal relationship are needed to examine this hypothesis.

In conclusion, a major issue regarding inhalant use is how previous exposure to volatile solvents alters subsequent responses to other drugs of abuse. The results of the present study demonstrate, for the first time, that re-

peated exposure to inhaled toluene produces cross-sensitization to behavioral and neurochemical responses to acute cocaine administration. Further research will be required to determine dose–effect relationships (e.g., lower doses of toluene), the time course of these phenomena and the specific neural mechanisms associated with these effects. However, the findings of the present study do support the recent conjecture that inhalants may alter subsequent responses to other drugs of abuse and, as such, may influence the likelihood to use and/or abuse other drugs (Schutz et al 1994; Johnson et al. 1995; Young et al. 1999).

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