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Enhancement of Postsynaptic Sensitivity to Dopaminergic Agonists Induced by Neonatal Hippocampal Lesions

Rui-Qian Wan, Ph.D., and Roy Corbett, Ph.D.

The effects of neonatal hippocampal lesions on behavioral responsiveness to dopaminergic agonists and antagonists were examined. The ventral hippocampus was damaged bilaterally using ibotenic acid on postnatal day 7, and locomotor responses to dopaminergic agonists and antagonists were evaluated on postnatal day 35 (PD35), 56 (PD56), and 70 (PD70). Quinpirole (0.06, 0.125, 0.25, and 0.5 mg/kg SC), but not SKF38393 (5 and 10 mg/kg SC), increased locomotion in a dose-dependent manner in control and lesioned groups on PD35 and PD56. However, lesioned rats displayed a greater behavioral response to quinpirole than controls at the doses of 0.25 and 0.5 mg/kg on both PD35 and PD56. Amphetamine (1.5 mg/kg IP) increased locomotor activity in both groups on PD70, but this effect was greater in lesioned rats than in controls. Raclopride (0.25 and 0.5 mg/kg SC) and SCH23390 (0.01 and 0.02 mg/kg SC) blocked the amphetamine-induced hyperlocomotion in the lesioned and control groups. These results suggest that neonatal hippocampal lesion-induced behavioral hyperresponsiveness to amphetamine is likely related to an increased postsynaptic sensitivity of the D_2 subtype of receptors. ***[Neuropsychopharmacology 16:259–268, 1997]*** *© 1997 American College of Neuropsychopharmacology*

KEY WORDS: *Amphetamine; Dopamine D_1; Dopamine D_2; Hippocampus; Locomotion; Neonatal lesions; Neurotoxin*

Abnormal neurodevelopmental processes may be involved in some aspects of schizophrenia (Weinberger 1987; Mednick et al. 1991; Kerwin and Murray 1992; Bloom 1993). Clinical studies have suggested that regional neuropathology during early development may result in behavioral abnormalities in later life (Weinberger 1987; Bloom 1993; Kotrla and Weinberger 1994). Neuropathological changes in the hippocampus have been described in schizophrenic brains (Brown et al. 1986; Falkai and Bogerts 1986; Beckmann et al. 1987; Bogerts 1993; Randolph et al. 1993; Hall et al. 1994). The hippocampus is anatomically interconnected with many structures in the mesolimbic and mesocortical dopamine (DA) systems (Groenewegen et al. 1991). Hippocampal glutamatergic efferents and dopaminergic efferents from the ventral tegmental area (VTA) converge onto the same neurons in the nucleus accumbens (NAc) (Totterdell and Smith 1989; Groenewegen et al. 1991). This hippocampal–accumbens interaction has been postulated to play an important role in modulating motor behaviors. Rats with hippocampal lesions become highly susceptible to environmental stimulation and psychomotor stimulants such as amphetamine. Thus, hippocampal lesions have been used to produce an animal model for the study of schizophrenia (McKinney and Moran 1981; Schmajuk 1987; Grey et al. 1991; Whishaw and Mittleman 1991).

A series of studies examining the effects of neonatal hippocampal lesions on behavior at different ages in rats has been reported (Lipska and Weinberger 1993;

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Lipska et al. 1993, 1995a, 1995b). Neonatal lesions of the hippocampus were found to induce delayed behavioral impairments that resulted in a hyperresponsiveness to stress and amphetamine at postnatal day 56 (PD56), but not at postnatal day 35 (PD35; Lipska et al. 1993). In rats PD35 and PD56 correspond to puberty and early adulthood, respectively (Ojeda et al. 1980). A previous in vivo microdialysis study of freely moving rats in our laboratory indicated that although amphetamine induced greater locomotion in rats with neonatal hippocampal lesions than in controls, the level of extracellular DA in the NAc was similar in both lesioned and control rats (Wan et al. 1996). This dissociation between an enhanced behavioral responsiveness and a lack of increase in DA release from presynaptic terminals suggested that an increased postsynaptic sensitivity may play an important role in these behavioral impairments. In addition, another study indicated that rats with neonatal hippocampal lesions were behaviorally hyperresponsive to apomorphine, a nonselective DA receptor agonist, at puberty and early adulthood (Lipska and Weinberger 1993). However, the role of the specific subtype of DA receptors in this lesion-induced hypersensitivity has not been identified. Thus, the present study was designed to identify the specific DA receptor subtype that is involved in the mediation of behavioral hyperresponsiveness induced by neonatal hippocampal lesions. Our experiments examined the lesion-induced effect on locomotor responsiveness to D_1 and D_2 receptor agonists and antagonists at different ages.

MATERIALS AND METHODS

Subjects

Pregnant Sprague-Dawley rats (Charles River) were obtained at 12 to 15 days of gestation. The rats were housed individually and maintained under the standard laboratory conditions as outlined in the "NIH Guide for the Care and Use of Laboratory Animals" (National Institute of Health Publications, No. 85-23, revised 1985) with 12-hour dark–light cycle. Food and water were available ad libitum. Male pups in each litter were used for the experiments. Pups were weaned on postnatal day 25 and grouped two to three per cage according to their surgical status. To maintain a mixed sexual environment for growing pups, two female pups were kept in each litter until weaning. There were 128 male rats included in this study, which were from approximately 24 litters.

Surgery

Neonatal hippocampal lesions were produced in male pups on postnatal day 7 (PD7). Litters that had four to six male pups were selected for the experiments. The half of the pups in each litter was randomly assigned to the lesioned group. The other half of the pups was the control group.

Bilateral lesions of the ventral hippocampus were performed using a method described previously (Lipska et al. 1993; Wan et al. 1996). Briefly, each of the anesthetized pups (hypothermia on wet ice for about 15 min) was placed on a platform that was fastened on a stereotaxic apparatus. The head of the pup was loosely fixed on the platform and the skull was kept flat. After an incision was made in the skin, two injectors made of 32-gauge hypodermic tubing were used to deliver drug solution or vehicle. Ibotenic acid (IBO, Sigma, St. Louis, MO) was prepared in 0.1 M phosphate buffered saline (PBS, pH 7.4) in the concentration of 10 μg/μl. A volume of 0.3 μl/side of IBO (lesions) or the same volume of PBS (controls) was infused bilaterally into the ventral hippocampus using the stereotaxic coordinates AP −3.0, ML ± 3.5, and DV −4.0 mm relative to bregma. The flow rate of infusion was 0.15 μl/minute. After completion of infusion the injectors remained in the places for another 4 minutes. The incision was closed with two clips. The pup was then placed on a warm water heating pad (American Medical Systems, Cincinnati, OH) at 37° C and returned to its mother after its body temperature recovered.

Locomotor Apparatus and Behavioral Assessments

Each locomotor chamber (clear polycarbonate cage, 45 × 22 × 20 cm) was equipped with three photoelectric light sources spaced at 18-cm intervals and 1 cm above the grid floor to record horizontal movements. Consecutive interruptions of two separate light beams were registered as activity counts and summarized every 5 minutes by the microprocessor-based control system.

The behavioral tests examined spontaneous exploration, drug-influenced locomotor activity, and stereotyped behavior. For each rat, spontaneous locomotion was recorded during the first 60 minutes. At the end of this period, the rat was injected with either drug or vehicle and returned immediately to the chamber for another 60 minutes. All behavioral assessments took place between 9:00 A.M. and 2:00 P.M.. Stereotyped behaviors were assessed for 30 s every 10 minutes following injection. Their overall stereotypy was rated on a modified version of the scale that was originally described elsewhere (Maclennan and Maier 1983; Mittleman et al. 1993): 0, no stereotypy; 1, intermittent stereotypy; 2, continuous stereotypy over a wide area; and 3, continuous stereotypy in a restricted area.

Drugs and Experimental Groups

d-Amphetamine (Sigma, St. Louis, MO), (−)-Quinpirole [Research Biochemicals International (RBI), Nat-

ick, MA], (±)-SKF-38393 (RBI), SCH-23390 (RBI), and Raclopride (ASTRA, Sodertalje, Sweden) were prepared in saline and administered in an injection volume of 1 ml/kg. The doses of drugs used in the present study were selected based on the previous studies and our own preliminary experiments (Mittleman et al. 1993; Petry et al. 1993; Wan et al. 1996).

On PD35, rats were examined for their behavioral responses to quinpirole (0 (saline), 0.06, 0.125, 0.25, and 0.5 mg/kg SC) and SKF (5 and 10 mg/kg SC). Rats in the same lesion status were randomized to each group of the different drugs and doses (n = 8 at each of the doses for every drug). Rats from the same litter were randomly distributed to different groups.

On PD56, all of the rats were examined again for their behavioral response to quinpirole and SKF at the same doses used on PD35. Groups of the different drugs and doses (n = 8/group) were formed randomly from rats in the same lesion status. However, the new assignment was made so that each of the rats was tested with a drug or a dose different from that it had received on PD35. Again, rats from the same litter were assigned to different groups. In addition, a new group of controls and a group of lesioned rats (n = 8/group) were added to examine behavioral responses to quinpirole (0.125 mg/kg) in combination with SKF (10 mg/kg). SKF was injected 10 minutes prior to quinpirole. These two groups were not tested previously.

On PD70, six groups of controls and six groups of lesioned rats (n = 8/group) were randomly formed from rats that had been tested on PD35 and PD56. This experiment examined the effects of raclopride (0.25 and 0.5 mg/kg SC) and SCH (0.01 and 0.02 mg/kg SC) on amphetamine-induced (1.5 mg/kg IP) locomotion. Raclopride or SCH was injected 10 minutes prior to the injection of amphetamine.

Histology

At the end of the behavioral assessments, each rat was anesthetized with Nembutal (pentobarbital sodium injection, USP) and perfused transcardially with 4% formalin-PBS solution. The brain was removed from the skull. After further fixation in formalin solution, the brain was sliced with a freezing cryostat. The sections through the damaged area were saved, mounted, and stained with cresyl violet. Each section was examined under a microscope to determine the location and extent of lesions.

Statistics

Repeated-measures analysis of variance (ANOVA) was used to analyze behavioral data. Neuman–Keuls post-hoc comparisons and Dunnett's t-tests were used when appropriate to identify a significant difference between groups.

RESULTS

Histology

Bilateral damage to the hippocampus occurred consistently in all rats. The place and size of lesions were similar to that of our previous study (Wan et al. 1996). Figure 1 provides an example of neonatal hippocampal damage. Substantial lesions were observed in the ventral hippocampus that included the CA1, CA3, and dentate gyrus. The lesions were indicated by cavitation, cell loss, and neuroglial proliferation (Figure 2). The dorsal part of the hippocampus, including the CA1, CA3, and dentate gyrus, was generally spared in most of the rats. Isolated small pieces of the ventral dentate, CA3, or CA1 were spared in some rats. Damage to the subiculum was indicated in the posterior portion of the hippocampus in most of the rats. Small damage to the entorhinal and piriform cortices was present in a few rats. However, damage to the adjacent thalamic areas was not detected.

Behavior

Spontaneous Exploration. Spontaneous exploration as indicated by locomotor activity before injections was not different between control and lesioned groups on PD35 and PD56. An example of similar spontaneous locomotion between two groups is illustrated in Figure 3.

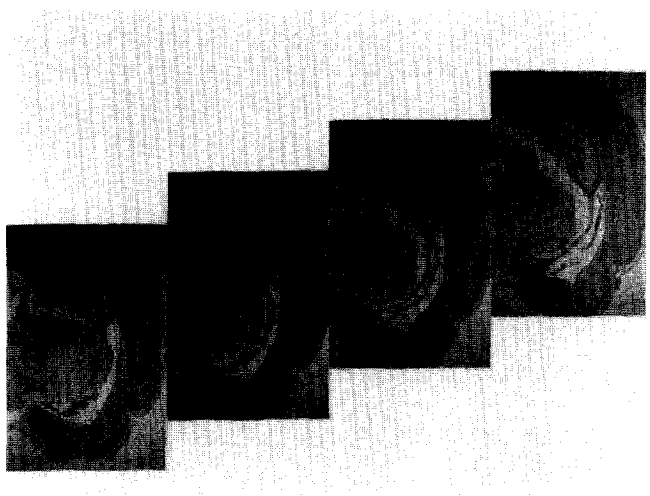

Figure 1. Coronal sections that indicate the place and size of neonatal hippocampal lesions produced by ibotenic acid. Sections were stained with cresyl violet. Anteroposterior atlas coordinates for these coronal sections (from left to right) correspond roughly to −4.30 to −5.30 mm posterior to bregma (Paxinos and Watson 1986).

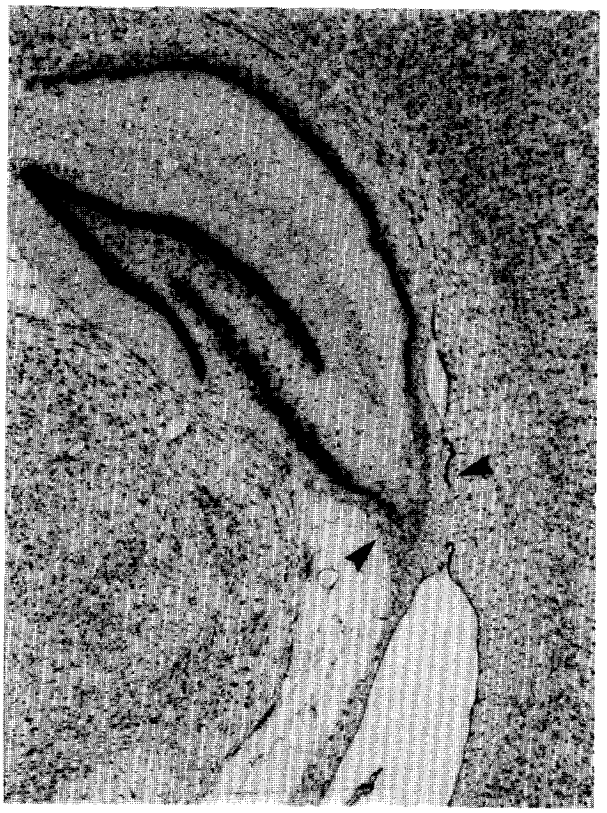

Figure 2. Cresyl violet–stained coronal section that indicates ibotenic acid-induced lesions in the hippocampus. Damage is indicated by cavitation, cell loss, and neuroglial proliferation. *Arrows*, focal neuronal loss and neuroglial proliferation in the CA2 and CA3 areas. The major part of the dorsal hippocampus is generally spared.

This similar spontaneous exploration between the control and lesioned groups was indicated in the experiments that examined the effects of raclopride and SCH on amphetamine-induced locomotor activity on PD70 as well.

Effect of Quinpirole. Administration of saline did not influence locomotor activity in either group on PD35 and PD56 (Figure 3). Quinpirole increased the locomotor activity for both groups in a dose-dependent manner (dose, PD35: $F_{4,70} = 16.73$, $p < .001$; PD56: $F_{4,70} = 10.25$, $p < .001$). At the lowest dose (0.06 mg/kg), quinpirole suppressed locomotion in both groups relative to saline on both PD35 and PD56 (drug, PD35: $F_{1,28} = 21.54$, $p < .01$; PD56: $F_{1,28} = 27.66$, $p < .01$). Hippocampal lesions influenced the locomotor response to quinpirole (lesion, PD35: $F_{1,70} = 11.78$, $p < .01$; PD56: $F_{1,70} = 8.86$, $p < .01$; lesion × dose ($F_{4,70} = 3.32$, $p < .05$). At the doses of 0.25 and 0.5 mg/kg, the lesioned group had greater locomotor activity than the control group on PD35 and PD 56 (Figure 3).

Intermittent stereotyped behavior occurred only following the highest dose of quinpirole (0.5 mg/kg). The frequency of sniffing and rearing behaviors increased on both PD35 and PD56. However, the scores of stereotyped behavior in the lesioned group did not differ from the control group. Both groups exhibited a significant effect of time for the occurrence of stereotyped behavior during the 60 minutes following injection (time, $F_{5,140} = 6.03$, $p < .01$; Figure 3, inserts).

Effect of SKF-38393. SKF alone at two doses (5 and 10 mg/kg) did not significantly alter locomotor activity or stereotyped behavior in either group on PD35 and PD56. Lesioned rats did not display a behavioral hypersensitivity to SKF as compared to controls (data not shown).

Effect of Quinpirole in Combination with SKF-38393. Quinpirole (0.125 mg/kg) in combination with SKF (10 mg/kg) markedly enhanced locomotor activity in the lesioned group but not the control group (lesion, $F_{1,28} = 4.99$, $p < .05$; lesion × drug, $F_{1,28} = 5.02$, $p < .05$; lesion × drug × time, $F_{11,308} = 2.35$, $p < .01$, Figure 4). For the lesioned group, quinpirole (0.125 mg/kg) or SKF (10 mg/kg) alone did not significantly increase locomotion compared to saline, although the quinpirole-induced locomotor activity did show a significant effect over time compared to saline (time, $F_{11,154} = 3.41$, $p < .001$; drug × time, $F_{11,154} = 4.22$, $p < .001$). Following combined administration of quinpirole and SKF, the locomotor activity of lesioned rats was higher than saline (drug, $F_{1,14} = 5.74$, $p < .05$; drug × time, $F_{11,154} = 6.06$, $p < .001$) and SKF (drug, $F_{1,14} = 4.78$, $p < .05$; drug × time, $F_{11,154} = 5.01$, $p < .001$). However, the locomotion induced by the combined injection did not significantly differ from that induced by quinpirole alone.

Stereotyped behavior was observed only following injections of quinpirole in combination with SKF (drug, $F_{3,56} = 38.04$, $p < .001$; time, $F_{5,280} = 14.65$, $p < .01$; drug × time, $F_{15,280} = 14.66$, $p < .01$, Figure 4, inserts). Stereotypy occurred more frequently in the lesioned group than the control group (lesion, $F_{1,56} = 26.84$, $p < .01$; lesion × drug × time, $F_{15,280} = 9.41$, $p < .01$).

Effect of Raclopride on Amphetamine-Induced Locomotion. Amphetamine (1.5 mg/kg) enhanced locomotor activity in both groups (drug, $F_{1,28} = 50.55$, $p < .001$, Figure 5). The lesioned group had a higher locomotor response to amphetamine than the control group (lesion, $F_{1,28} = 4.78$, $p < .05$; lesion × drug, $F_{1,28} = 6.12$, $p < 0.05$; lesion × drug × time, $F_{11,308} = 5.02$, $p < .001$). Raclopride at both doses (0.25 and 0.5 mg/kg) abolished amphetamine-enhanced locomotion in both groups. For both groups, the locomotor activity following injections of raclopride in combination with amphetamine was significantly lower than that treated with amphetamine alone (p's $< .001$), and no difference was observed compared to saline. In lesioned rats, the locomotor activity following combined amphetamine and raclopride injection at the lower dose (0.25 mg/kg) increased during the later test session, which was indicated by a significant time effect during the

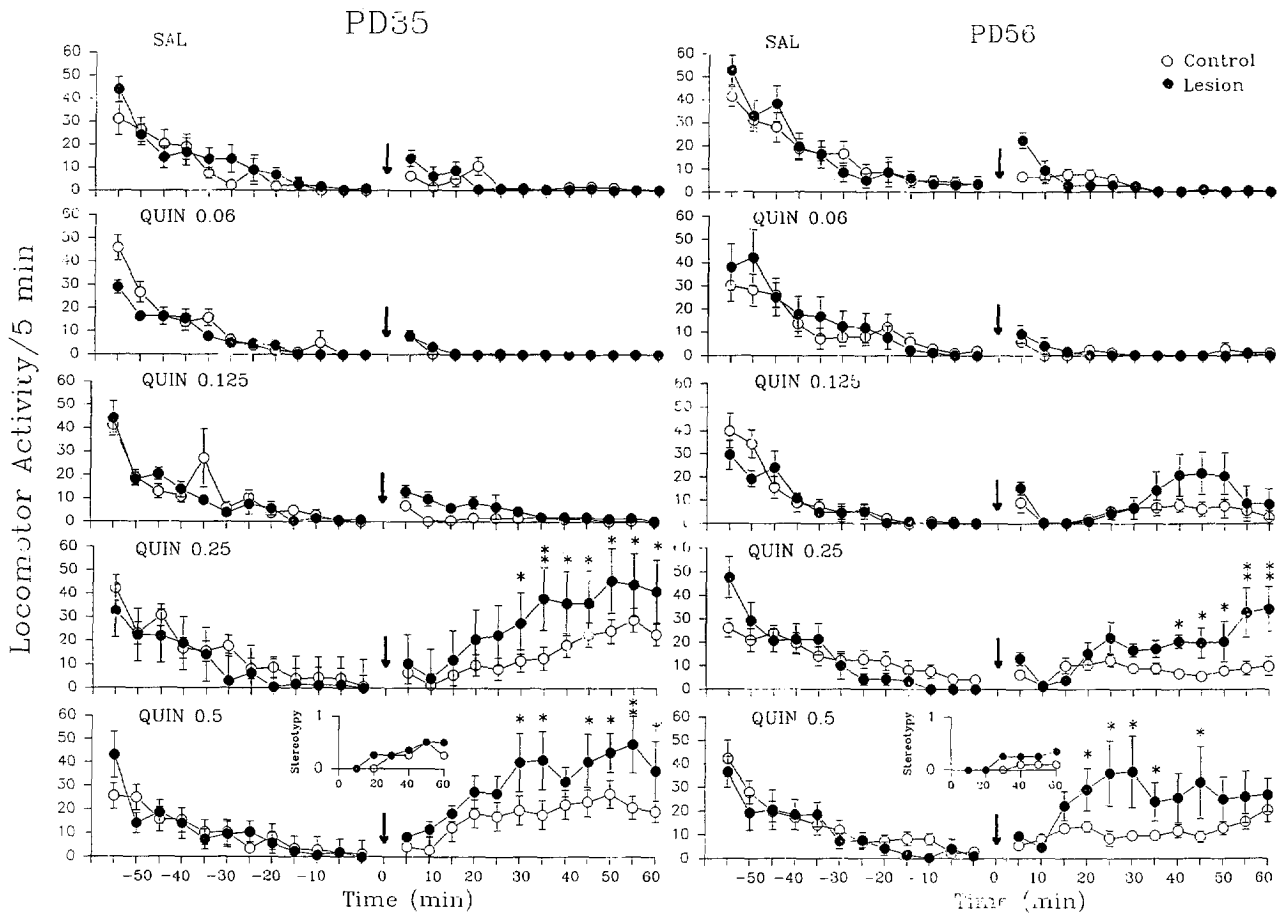

Figure 3. Effect of neonatal hippocampal lesions on quinpirole-induced locomotion (*main graphs*) and stereotyped behavior (*inserts*) on PD35 and PD56. Left panel, behavioral responses examined on PD35; *right panel*, behavioral responses examined on PD56; *symbols* (*Open circles*, controls; *solid circles*, lesions), mean; *vertical bars*, SEM. *Vertical arrows*, time of injection. $^{**}p < .01$; $^{*}p < .05$ versus controls.

60-min period (time, $F_{11,154} = 2.83$, $p < .01$; drug × time, $F_{11,154} = 5.92$, $p < .001$, Figure 5, right panel).

Stereotyped behavior was found only following administration of amphetamine alone in both groups (drug, $F_{3,56} = 115.71$, $p < .001$; time, $F_{5,280} = 25.73$, $p < .001$; drug × time, $F_{15,280} = 25.73$, $p < .001$, Figure 5, inserts). The score of stereotypy was higher in the lesioned group than the control group (lesion, $F_{1,56} = 20.23$, $p < .001$; lesion × drug × time, $F_{15,280} = 6.25$, $p < .01$). Raclopride at both doses suppressed stereotyped behavior induced by amphetamine.

Effect of SCH-23390 on Amphetamine-Induced Locomotion. SCH at both doses (0.01 and 0.02 mg/kg) also abolished amphetamine-induced hyperlocomotion in both groups (p's < .001, Figure 6). The locomotor activity following SCH in combination with amphetamine did not differ from saline.

SCH at both doses also completely suppressed the amphetamine-induced stereotyped behavior (Figure 6, inserts). Rats injected with the higher dose of SCH (0.02 mg/kg) were inactive during almost the entire test session.

DISCUSSION

Enhancement of Postsynaptic Sensitivity Induced by Neonatal Hippocampal Lesions

Hippocampal–accumbens interaction has been identified as important in modulating psychomotor activity. The effects of hippocampal lesions on DA release from presynaptic terminals in the NAc have been examined using in vivo microdialysis. Bilateral hippocampal lesions made in adult rats induced locomotor hyperresponsiveness to amphetamine, and this behavioral impairment was related to an increased amphetamine-stimulated DA release in the NAc (Wilkinson et al. 1993). However, our previous microdialysis study in freely moving rats indicated that neonatal hippocampal lesions had no effect on amphetamine-induced DA release in the NAc at PD56, although lesioned rats did show a higher locomotor response to amphetamine than did controls (Wan et al. 1996). These results suggest that neonatal hippocampal lesion-induced behavioral hyperresponsiveness to amphetamine may be related to a postsynaptic DA receptor supersensitivity.

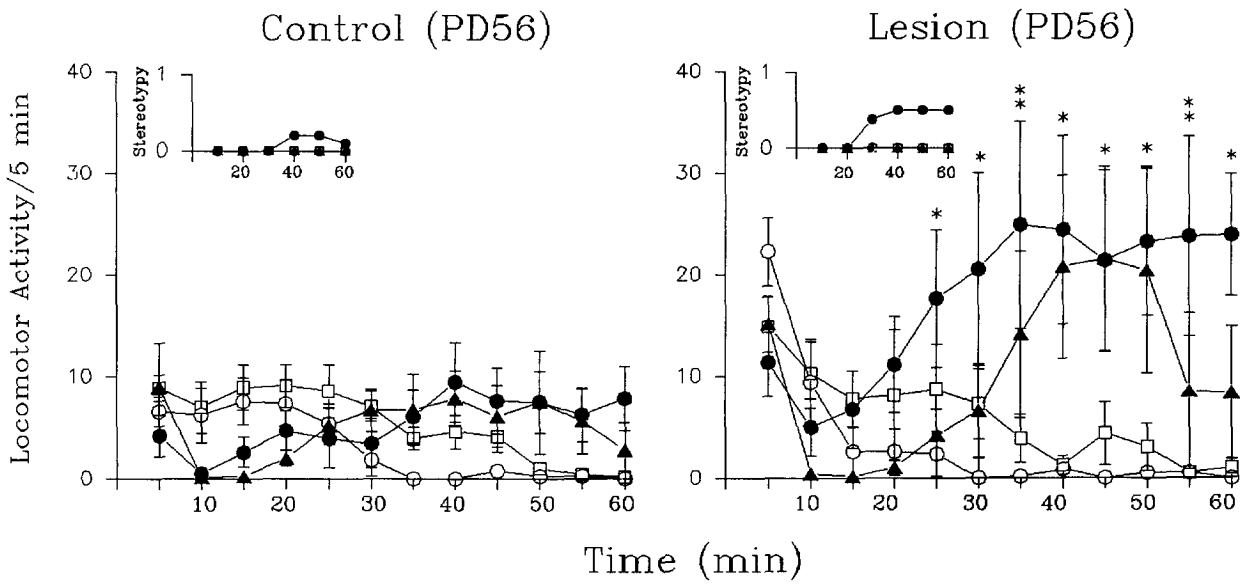

Figure 4. Effect of neonatal hippocampal lesions on locomotion (*main graphs*) and stereotyped behavior (*inserts*) induced by quinpirole (*triangles*, 0.125 mg/kg) or SKF38393 (*squares*, 10 mg/kg) alone versus coadministration of quinpirole and SKF38393 (*solid circles*) on PD56. *Left panel*, behavioral responses in control rats; *right panel*, behavioral responses in lesioned rats; (*open circles*, saline) *symbols*, mean; *vertical bars*, SEM. $^{**}p < .01$; $^{*}p < .05$ versus control rats that received coadministration. See text for other comparisons among treatment.

The present study provides evidence for enhanced postsynaptic DA receptor sensitivity following neonatal hippocampal lesions. The results indicated that quinpirole at the low dose (0.06 mg/kg) decreased locomotion, which was likely due to stimulation of presynaptic autoreceptors (Imperato et al. 1988; Eilam and Szechtman 1989; Barnes et al. 1990; Mogenson and Wu 1991), whereas higher doses (0.25 and 0.5 mg/kg) increased

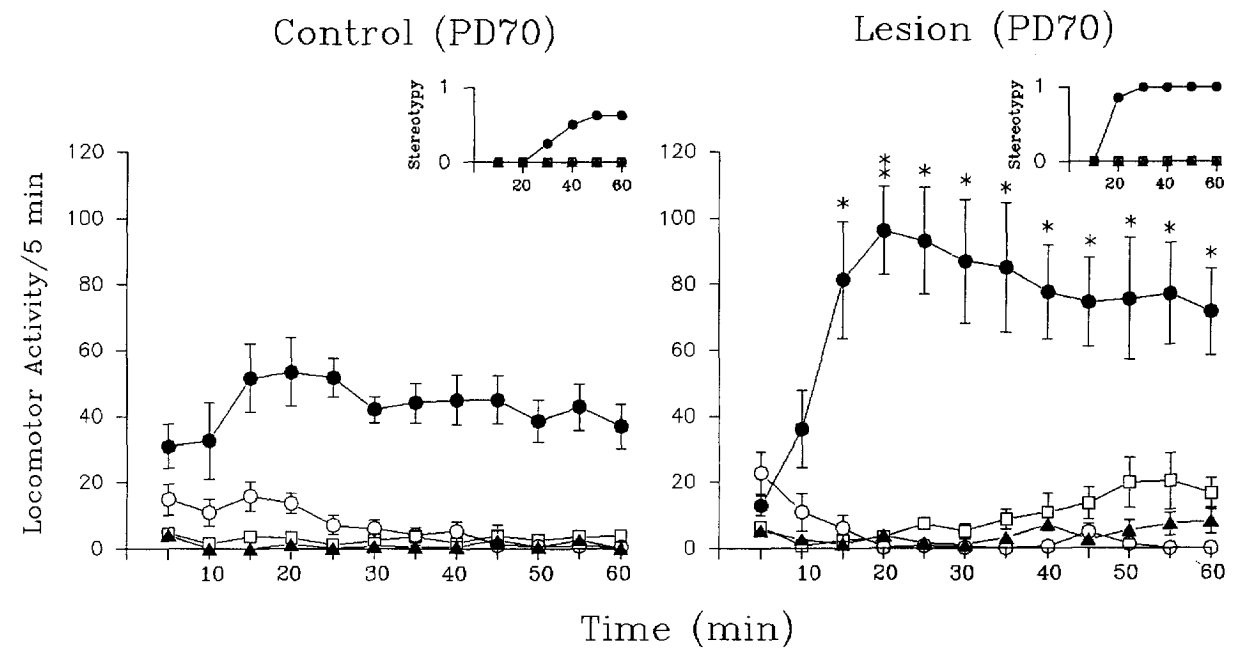

Figure 5. Effect of neonatal hippocampal lesions on locomotion (*main graphs*) and stereotyped behavior (*inserts*) induced by amphetamine (*solid circles*, 1.5 mg/kg) alone versus coadministration of amphetamine (1.5 mg/kg) and raclopride (*squares*, 0.25 mg/kg; *triangles*, 0.5 mg/kg) on PD70. *Left panel*, behavioral responses in control rats; *right panel*, behavioral responses in lesiond rats; *open circles*, saline; *symbols*, mean; *vertical bars*, SEM. $^{**}p < .01$; $^{*}p < .05$ versus control rats that received amphetamine. See text for other comparisons among treatments.

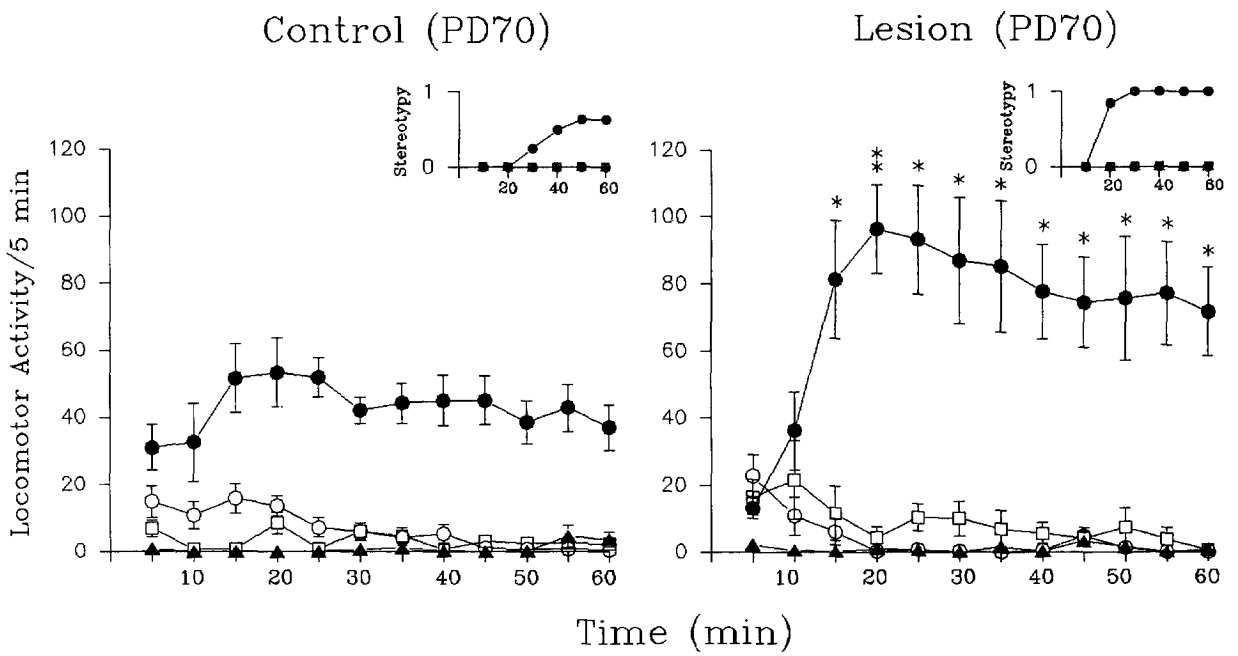

Figure 6. Effect of neonatal hippocampal lesions on locomotion (*main graphs*) and stereotyped behavior (*inserts*) induced by amphetamine (*solid circles*, 1.5 mg/kg) alone versus coadministration of amphetamine and SCH23390 (*squares*, 0.01 mg/kg and *triangles*, 0.02 mg/kg) on PD70. *Left panel*, behavioral responses in control rats; *right panel*, behavioral responses in lesioned rats; *open circles*, saline; symbols, mean; *vertical bars*, SEM. $^{**}p < .01$; $^{*}p < .05$ versus control rats that received amphetamine. See text for other comparisons among treatments.

locomotor activity. These results were consistent with previous reports that quinpirole produced a biphasic effect on locomotion with respect to dose and time course (Eilam and Szechtman 1989; Van Hartesveldt et al. 1992). Of particular importance, however, was the fact that rats with neonatal hippocampal lesions had a behavioral hypersensitivity to quinpirole. This neonatal lesion-induced behavioral impairment was observed in rats at both PD35 and PD56.

The increase in locomotion induced by higher doses of quinpirole may be attributable to its postsynaptic stimulation (Van Hartesveldt et al. 1992; Braun et al. 1993; Yue et al. 1994). One explanation for quinpirole-induced hyperlocomotion could be the production of an active metabolite based on the late onset of hyperactivity following systemic injection of quinpirole (Gonzalez-Lima et al. 1987; Eilam and Szechtman 1989). Previous studies, however, have suggested that quinpirole at higher doses may directly stimulate postsynaptic D_2 receptors. The NAc is one of the regions that has a high density of D_2 receptors in the rat brain (Gehlert and Wamsley 1985; Gehlert et al. 1992). Intraaccumbens injections of quinpirole produced an early decrease followed quickly by an increase in locomotor activity (Van Hartesveldt et al. 1992). This behavioral biphasic effect induced by quinpirole was similar to that produced by intraaccumbens injections of DA with respect to the time course of the behavioral response (Wachtel et al. 1979). The similarity in the behavioral profiles suggests that quinpirole and DA are alike in their direct stimulation of pre- and postsynaptic DA receptors.

Although our results from microdialysis and behavioral studies suggest that neonatal hippocampal lesions increase the sensitivity of postsynaptic DA receptors, it remains unclear whether this hypersensitivity is the result of an increase in the density of DA receptors. Two independent studies of DA receptor binding using similar neonatal hippocampal lesions have reported inconsistent results. One study indicated that the density of D_3 receptors was lower in the NAc and that the density of D_1 receptors was higher in the caudate putamen, with no change in D_2 receptors in lesioned rats (Flores et al. 1996). The other study showed that the lesions did not alter D_2/D_3 and, D_4 receptor densities in the dorsolateral and ventrolateral striatum and the NAc (Knable et al. 1994). However, this latter study might not rule out an alteration in D_3 receptors because the study did not distinguish between the D_2 and D_3 receptor subtypes. A decrease in D_3 receptors could have been masked by changes in D_2 receptors. Postsynaptic D_3 receptors have been shown to be involved in the modulation of locomotor activity. U99194A, a D_3 antagonist, increases locomotion, suggesting that D_3 receptors may exert an inhibitory influence on psychomotor activity (Waters et al. 1993, 1994). Moreover, previous binding studies have shown that quinpirole and raclopride bind to the

D_3 receptor subtype in addition to the D_2 receptor subtype (Gehlert et al. 1992; Seeman and Van Tol 1994). These data suggest that quinpirole-induced hyperlocomotion in neonatal hippocampally lesioned rats may be related not only to a stimulation of D_2 receptors but also to a decrease in the inhibitory effect of D_3 receptors.

Roles of D_1 and D_2 Receptors in Lesion-Induced Hypersensitivity

Increased sensitivity of the D_2 subtype of DA receptors may play an important role in neonatal hippocampal lesion-induced behavioral impairments. Two results in this study support this conclusion. First, the lesioned group showed a behavioral hypersensitivity to quinpirole indicated by hyperlocomotion induced by quinpirole alone in a dose-dependent manner in lesioned rats relative to controls. In contrast, rats with neonatal hippocampal lesions did not show behavioral hypersensitivity to SKF that alone had no significant effect on locomotion in either group. The dosages of SKF (5 and 10 mg/kg) were found in previous studies to be sufficient to produce effects of SKF on locomotor or stereotyped activities (Eilam et al. 1992; Mittieman et al. 1993). However, we cannot rule out the possibility that SKF alone at a higher dose than 10 mg/kg might induce differential effects on behavioral responses in lesioned rats compared to controls. Second, raclopride diminished the amphetamine-induced hyperlocomotion and stereotyped behavior. Evidence has suggested that D_2 receptors may play a primary role in mediating activity of hippocampal accumbens neurons. A previous study indicated that iontophoretic applications of quinpirole or the D_2 antagonist sulpiride, but not the D_1 antagonist SCH23390, altered excitability of hippocampal accumbens neurons (Yang and Mogenson 1986). Thus, it is likely that the sensitivity of D_2 receptors in the hippocampal accumbens system may be altered because of a degeneration of hippocampal projections to the NAc following neonatal hippocampal lesions. Similar impairments of D_2-mediated behaviors have been demonstrated in rats with hippocampal lesions made in adulthood (Mittleman et al. 1993).

Even though D_1 and D_2 receptors can produce opposite effects on some behavioral and neurochemical responses (Eilam et al. 1991, 1992), activation of both D_1 and D_2 receptors has been shown to be necessary to achieve the full range of expression of DA-mediated behaviors (Clark and White 1987; Waddington 1989; Walters et al. 1987). Previous studies have indicated that coadministration of D_1 and D_2 agonists produced synergistic effects on behavioral responses, effects that could not be induced by the activation of either receptor alone (Amalric et al. 1986; Barone et al. 1986; Molly et al. 1986; Robertson and Robertson 1986; White et al. 1988; Dreher and Jackson 1989). The results of the present study indicate that activation of D_1 receptors is necessary for amphetamine-induced behaviors because SCH abolished amphetamine-induced hyperlocomotion in both control and lesioned groups. These results are consistent with those of the previous studies (Molly et al. 1986; Petry et al. 1993). In the present study, however, coadministration of quinpirole and SKF did not significantly increase locomotion in control rats. This lack of effect may be attributed to the doses of the two drugs administered and to the differences in experimental methodology between the present and previous studies (Dreher and Jackson 1989; White et al. 1988). Of importance was that coadministration of both quinpirole and SKF significantly increased locomotion only in lesioned rats compared to the treatment with saline or SKF alone. Although this effect was not significantly higher than that produced by quinpirole alone, the locomotor response following coadministration of the two drugs had a more rapid onset and a longer duration than that produced by quinpirole alone. This result provides additional evidence for the presence of neonatal hippocampal lesion-induced postsynaptic hypersensitivity of DA receptors.

In summary, the results of the present study extend previous findings indicating that there was no neonatal hippocampal lesion-induced effect on DA release in the NAc, although lesioned rats displayed locomotor hyperresponsiveness to amphetamine. The data from the present study indicate that behavioral hyperresponsiveness in lesioned rats is likely due to the enhanced postsynaptic sensitivity of D_2 receptors.

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