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Selective blockade of spontaneous motor stereotypy via intrastriatal pharmacological manipulation

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Abstract

Abnormal repetitive behavior, including stereotypy, is often observed in conjunction with developmental, neuropsychiatric, and genetic disorders. The present work employed the deer mouse model of spontaneous and persistent stereotypy to identify basal ganglia involvement in the mediation of these abnormal behaviors. To evaluate the hypothesis that stereotypy is expressed in these mice due to alterations in the activity of cortico-basal ganglia motor circuits, intrastriatal pharmacological manipulations aimed at attenuating the spontaneously emitted stereotypy were performed. Bilateral striatal infusion of the NMDA or dopamine D_1 receptor antagonists MK-801 or SCH23390, respectively, produced a substantial reduction in levels of stereotypic jumping without inhibiting nonstereotypic motor behavior. These findings support the hypothesis that environmentally related stereotypy is expressed as a consequence of elevated feedback activity occurring along motor circuits of the basal ganglia.

Keywords: Spontaneous stereotypy; Striatum; MK-801; SCH23390

1. Introduction

Abnormal stereotyped motor behavior is a phenomenon most commonly associated with developmental disorders such as autism and mental retardation (Bartak and Rutter, 1976; Berkson et al., 2001; Frankel et al., 1978; Lund, 1986; Sakuma, 1975). Stereotypy is also observed in conjunction with several neuropsychiatric and neurological disorders (Cath et al., 2001; McDougle et al., 2000), and is characteristic of the behavioral phenotype of certain genetic disorders, such as Lesch–Nyhan disease and Prader–Willi syndrome (Akefeldt and Gillberg, 1999; Ball et al., 1985; Clarke et al., 1996; Symons et al., 1999). In many of these clinical populations, stereotypies are manifested in forms such as body-rocking, hand-flapping, and skin-picking. Stereotypies are considered to be maladaptive not only because they can result in self-mutilation, but also because they interfere with sustained, goal-directed behaviors (Mason, 1991). An understanding of the pathophysiology underlying stereotyped behaviors would greatly facilitate the development of treatment options in these clinical populations.

Hypotheses regarding the neurobiological basis of stereotypy observed in clinical populations have relied largely on studies employing pharmacological induction of stereotypy in animals. These studies have established the involvement of several nuclei comprising cortico-basal ganglia–cortical feedback circuits in the mediation of drug-induced stereotypy. A consistent theme to these findings has been that manipulations known to elevate the positive feedback influence of the implicated motor circuit will induce or exacerbate stereotypy, whereas manipulations that suppress this feedback activity will attenuate such drug-induced behaviors.

Early experiments established the importance of the nigrostriatal dopamine pathway by showing that dopamine or a dopamine agonist injected into the corpus striatum induced stereotyped behavior in rats (Ernst and Smelik, 1966). Similarly, direct injections of opiate agonists into the substantia nigra produce intense stereotypies in rats (Iwamoto and Way, 1977), presumably due to disinhibition of nigrostriatal dopaminergic projections (Gale et al., 1979; Wood and Richard, 1982). Intrastriatal administration of the ionotropic glutamate receptor agonist, NMDA, induces stereotypic behavior, often indistinguishable from dopamine

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agonist-induced stereotypy. Likewise, it has been shown that systemic drug-induced stereotypy can be attenuated by intrastriatal administration of the NMDA receptor (NMDAR) antagonist, CPP (Bedingfield et al., 1997).

Intracortical manipulations enhancing the activity of excitatory cortico-striatal projections also exacerbate stereotypy levels. For instance, administration of the GABA antagonist, bicuculline, into the frontal cortex of rats enhances the motor-stimulatory effects of amphetamine, whereas amphetamine-induced stereotypy can be attenuated in rodents via intracortical infusion of DA or GABAergic agonists (Karler et al., 1998).

Manipulations known to modulate the activity of a primary output nucleus of the basal ganglia, the substantia nigra pars reticulata (SNpr), have also been shown to modulate stereotypic behavior. For example, direct infusion of GABA agonists into SNpr has been shown to induce stereotypy in rats (Scheel-Kruger et al., 1980). Additional support for a role of the SNpr in the mediation of stereotypy is provided by reports that 5-HT_2 antagonist microinjection into the subthalamic nucleus, a major excitatory afferent of the SNpr, suppresses apomorphine-induced stereotypy (Barwick et al., 2000).

Thus, stereotypic behavior can be exacerbated or attenuated via intracerebral manipulations that alter the activity of a cortico-basal ganglia–cortical motor feedback loop, and the studies cited previously have described certain chemoarchitectural mediators of acute drug-induced stereotypy. Clinically occurring stereotypy, however, is likely to be expressed as a result of long-term, experientially driven alterations in neuronal activity. Thus, an animal model that more closely approximates the clinical condition, such as one in which stereotypy is emitted spontaneously and persistently as a consequence of environmental factors, may be of particular value in identifying the clinically relevant neurobiological mechanisms of abnormal repetitive behavior. Our laboratory has recently adopted such a model (Powell et al., 2000). We have demonstrated that deer mice (*Peromyscus maniculatus*) develop high rates of spontaneous and persistent stereotyped behavior (jumping, backward somersaulting) when housed in standard laboratory cages.

In a previous study, we reported dissociation between spontaneously emitted and apomorphine-induced stereotypic topographies in these mice (Presti et al., 2002). Because this finding suggests that spontaneously emitted stereotypy may be mediated via neuronal mechanisms distinct from those involved in the mediation of drug-induced stereotypy, we wished to test the efficacy of pharmacological manipulations that have been reported to suppress drug-induced stereotypy to attenuate the spontaneous jumping stereotypy exhibited by deer mice. Thus, the present study sought to evaluate the hypothesis that the spontaneous stereotypy exhibited by caged deer mice is expressed as a consequence of hyperactivity along the implicated cortico-basal ganglia–cortical feedback circuit. To accomplish this objective, we employed intrastriatal pharmacological manipulation in freely moving deer mice exhibiting stereotyped jumping behavior. Specifically, we tested the hypothesis that striatal administration of selective glutamatergic and dopaminergic antagonists would selectively attenuate the spontaneous stereotypy exhibited by these mice.

2. Materials and methods

2.1. Animals

This study was performed using 32 stereotypic male ($n = 14$) and female ($n = 18$) deer mice. We have previously demonstrated that both male and female *P. maniculatus* (deer mice) develop high rates of persistent, spontaneously emitted stereotypy consisting of repetitive vertical jumping, backward somersaulting, or, to a lesser extent, patterned running when housed under standard laboratory conditions (Powell et al., 2000). Mice were group caged (three to four of the same sex mice per cage) in a standard ($29 \times 18 \times 13$ cm) laboratory mouse cage. Rodent chow and water were available ad libitum, and temperature was maintained at 24 °C. Mice were maintained on a 16/8-h light/dark cycle, with lights off at 0930 h. To assess the effects of intrastriatal drug administration on spontaneous stereotypy, we selected adult (>2 months old) mice demonstrating moderate to high levels of repetitive jumping during a 10-min, active cycle screening session. Mice exhibiting stereotypic somersaulting or patterned running (as opposed to repetitive jumping) were excluded from the study because these forms of behavior either interfered with the drug delivery apparatus (backward somersaulting), or were more difficult to quantify (patterned running).

2.2. Stereotaxic surgery

The mice were anesthesized using a ketamine (100 mg/ml) and acepromazine (10 mg/ml) cocktail administered by subcutaneous injection at a dose of 0.015 ml/g body weight. Using aseptic surgical technique, guide cannulae were implanted bilaterally into the dorsolateral striatum at the following coordinates: anterior to bregma 0.5 mm; lateral 2.5 mm; ventral −2.7 mm (see Franklin and Paxinos, 1997). The cannulae were fixed into place using ethyl-2-cyanoacrylate glue and dental cement. Animals were allowed to recover for at least 1 week prior to behavioral testing.

2.3. Drugs

The noncompetitive NMDAR antagonist, dizocilpine maleate (MK-801), and the selective D_1 dopamine receptor antagonist, SCH23390, were obtained from Sigma (St. Louis, MO). Both drugs were dissolved in artificial extracellular fluid (aECF: 145 mM NaCl, 1.2 mM $CaCl_2$, 2.7 mM KCl, 1.0

mM $MgCl_2$; pH 7.4). Drug dosages are expressed as micrograms per 0.5 μl per striatal hemisphere.

2.4. Behavioral testing

The effects of drug infusion were evaluated in freely moving deer mice. Drug or vehicle solution was drawn up through injectors into attached PE-20 tubing, connected at the far end to Hamilton microliter syringes that were mounted onto an inverted infusion pump. By attaching the vertically oriented pump to a swivel plate (a lazy susan), this injector system prevented the PE-20 tubing from twisting as a consequence of the high activity levels of the mice. Animals were captured and anesthesized with isofluorane in order to allow removal of obturators (which extended 1.2 mm beyond ventral extent of guide cannula) and insertion of internal injectors (which extended 1.0 mm beyond cannula). Injectors were held in place using modified obturator screw tops. After injectors were inserted, the mouse was transferred to its testing cage and monitored until it recovered from the gas (typically <1 min), after which videotaping began. The mouse was given 20 min to habituate to the testing conditions, after which an additional 20 min of baseline data was collected. Next, drug solution was infused over 60 s, and behavioral data were collected for an additional 30 min. Because drug was delivered to a freely moving, habituated animal, there was no handling-related stress associated with drug infusion, which can interfere with the activity of the drugs being delivered.

The experimental sessions were videotaped to allow for computer-assisted coding of observed behaviors. Behaviors were recorded continuously as mutually exclusive states by

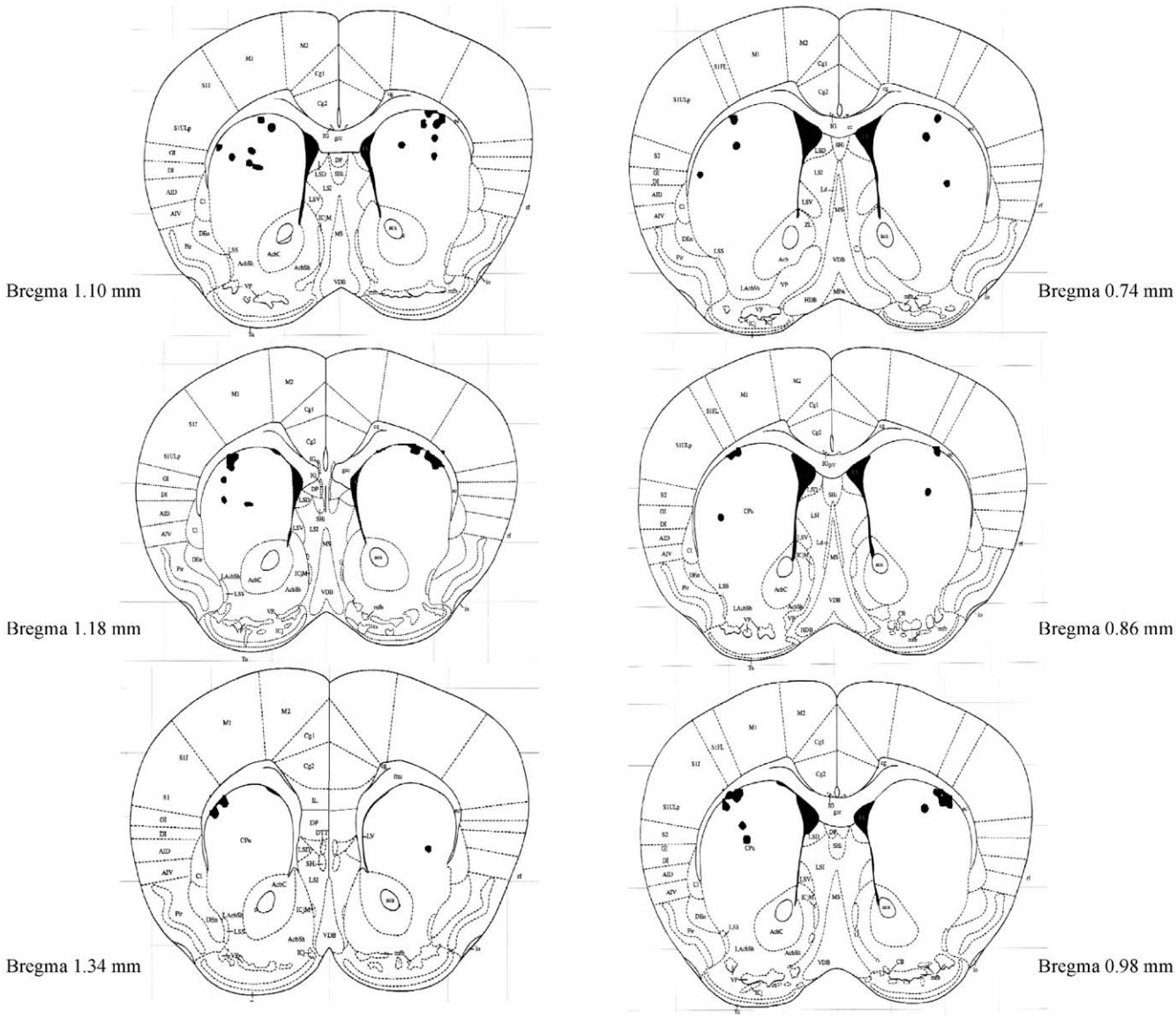

Fig. 1. Diagrammatic representation of cannulae tip placements in coronal sections.

trained observers and included jumping, locomotion, rearing, grooming, and burrowing. Interrater reliability was independently established at a κ level of 0.7, and testing sessions were coded using Observer software (Noldus) to determine the percentage of time the animals spent engaged in each of the recorded behaviors.

2.5. Experimental design and data analysis

Two experiments were conducted in the present study. The first experiment evaluated the effect of intrastriatal MK-801 administration on the behavior of stereotypic mice; the second evaluated the effect of intrastriatal SCH23390 in these mice. MK-801 was administered at 0.0, 1.5, or 2.75 μg/side; SCH23390 was administered at 0.0, 0.125, or 0.25 μg/side. Five to six subjects were assigned to each condition, with each mouse receiving only one treatment. One-way ANOVA was used to determine whether significant differences existed among vehicle and drug treatments, using percent time engaged in a specific behavior as the dependent measure. Post-hoc, pairwise comparisons were performed using Newman–Keuls analysis. For instances in which one-way ANOVA indicated a significant difference among treatments, comparisons of baseline and postinfusion behavioral data were also made for each of the treatment groups using a correlated *t* test.

2.6. Histology

Following completion of the in vivo drug experiment, the mouse brains were rapidly harvested and snap-frozen. Brain tissues were then sectioned into 20-μm slices and stained with cresyl violet. Cresyl violet-stained sections were examined under the microscope and the appropriate sections were placed in a register with a stereotaxic brain atlas to verify the coordinates of cannulae placement.

3. Results

3.1. Verification of cannulae placement

All of the cresyl violet-stained coronal sections revealed bilateral cannulae placement in the dorsal striatum. Although the dorsolateral striatum was targeted, some placements were found in more medial striatal positions. Cannulae placements are depicted in Fig. 1. No systematic

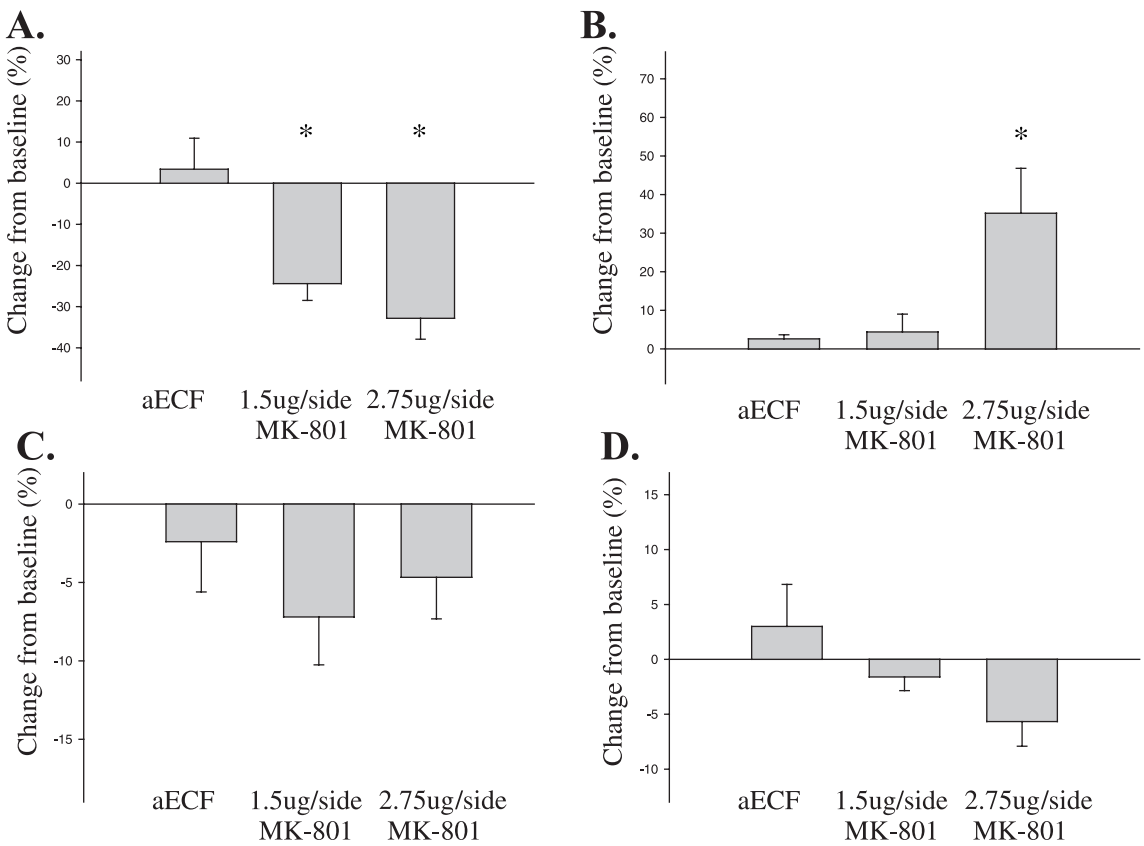

Fig. 2. Effects of intrastriatal MK-801 on mean levels of recorded behaviors. (A) Intrastriatal administration of MK-801 significantly attenuates spontaneous stereotypic jumping at 1.5 and 2.75 μg/side. (B) Normal locomotor activity is unaffected at 1.5 μg/side and significantly elevated at 2.75 μg/side MK-801. (C) No significant changes in the levels of rearing behavior were produced by either dose of MK-801. (D) Grooming activity was largely unaffected by MK-801. (Brackets represent standard error; * indicates that the effect was significantly different from vehicle at a significance level of $P < .05$.)

positional bias was associated with cannulae placements for any of the groups tested.

3.2. Effects of the NMDAR antagonist, dizocilpine maleate (MK-801)

Bilateral intrastriatal administration of MK-801 produced a substantial attenuation in stereotyped jumping relative to vehicle infusion (see Fig. 2) [$F(2,15) = 11.05$; $P = .002$]. Pairwise comparisons (Newman–Keuls) indicated that both the 2.75- and 1.5-μg/side doses of MK-801 produced a significant ($P < .05$) decrease in jumping stereotypy compared to vehicle. No difference was detected between the high and low doses of the drug. Comparison of baseline and postinfusion jumping levels using correlated t tests revealed that both 1.5 and 2.75 μg/side doses of MK-801 produced a significant attenuation in this behavior ($t = 6.06$, $df = 4$, $P = .004$ and $t = 6.46$, $df = 5$, $P = .001$, respectively), with mean levels falling from 30.0% to 5.4% and from 36.2% to 3.3%, respectively. No significant change in jumping levels was observed after vehicle administration, with mean levels rising marginally from 23.8% to 27.2% (data not shown).

Nonstereotyped motor behaviors, including locomotion, rearing, and grooming, were largely unaffected by intrastriatal administration of MK-801 at the doses tested. Although the ANOVA on locomotion data revealed a significant difference among treatment groups [$F(2,15) = 5.42$; $P = .02$], post-hoc pairwise comparisons indicated that only the high dose of MK-801 had a significant ($P < .05$) effect on the levels of locomotion compared to vehicle. As seen in Fig. 3, locomotor activity was significantly increased at this dose. The lower dose of MK-801, which was as effective as the higher dose in suppressing stereotypy, produced no significant changes in locomotion. Comparison of baseline and postinfusion locomotion levels using correlated t tests revealed that only the 2.75-μg/side dose of MK-801 produced a significant elevation in this behavior ($t = 3.02$, $df = 5$, $P = .03$), with mean levels rising from 10.4% to 45.5%. No significant changes were detected between baseline and postinfusion locomotion levels following vehicle and 1.5 μg/side MK-801 treatments, with levels rising from 4.8% to 7.4% and from 7.6% to 13.2%, respectively (data not shown).

Kruskal–Wallis one-way ANOVA on ranks indicated that neither dose of MK-801 had a significant effect on

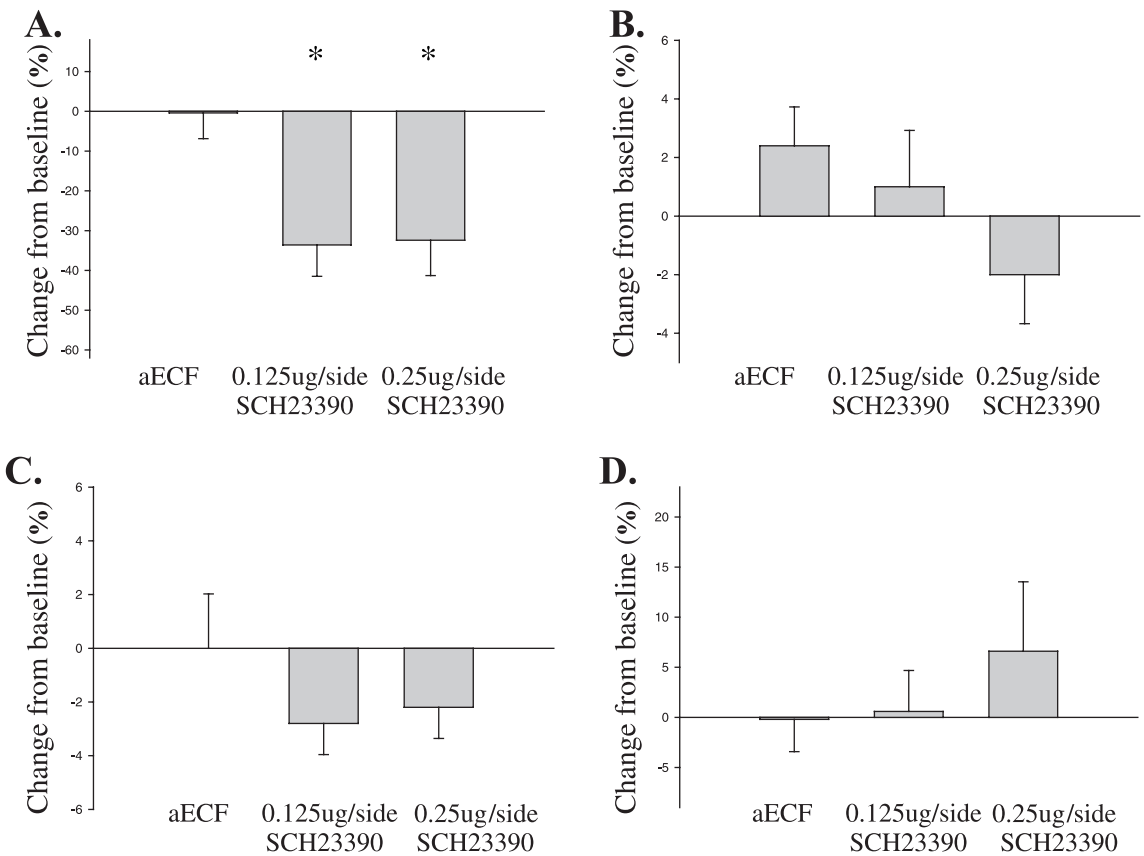

Fig. 3. Effects of intrastriatal SCH23390 on mean levels of recorded behaviors. (A) Intrastriatal administration of SCH23390 produced a significant attenuation of spontaneous jumping stereotypy at doses of both 0.125 and 0.25 μg/side. (B) Locomotor activity was not suppressed by intrastriatal administration of SCH23390 at doses that significantly attenuated stereotypy. (C) No significant changes in the levels of rearing behavior were produced by either dose of SCH23390. (D) Grooming activity was largely unaffected by SCH23390. (Brackets represent standard error; * indicates that the effect was significantly different from vehicle at a significance level of $P < .05$.)

rearing behavior [$H(2) = 2.26$; $P = .32$]. Similarly, grooming behavior was not significantly affected by either dose of the drug [$H(2) = 4.83$; $P = .09$].

3.3. Effects of the D_1 dopamine antagonist, SCH23390, on stereotyped behavior

A significant attenuation of stereotypic jumping was achieved at doses of SCH23390 that did not otherwise affect motor activity. Specifically, an ANOVA detected a significant difference among treatment groups in the levels of stereotyped jumping [$F(2,14) = 5.81$; $P = .02$]. Subsequent pairwise comparisons using Newman–Keuls revealed that both the 0.125- and 0.25-μg/side doses of SCH23390 produced a statistically significant ($P < .05$) attenuation in jumping stereotypy as compared to vehicle, but that no significant differences existed between the high and low doses. Comparison of baseline and postinfusion jumping levels using correlated t tests revealed that both 0.125 μg and 0.25 μg/side doses of SCH23390 produced a significant attenuation in this behavior ($t = 4.219$, $df = 4$, $P = .01$ and $t = 3.52$, $df = 4$. $P = .02$, respectively), with mean levels falling from 52.4% to 19.0% and from 43.6% to 11.8%, respectively. No significant change in jumping was observed after vehicle administration, with mean levels changing slightly from 25.3% to 23.2% (data not shown).

No statistically significant alterations in nonstereotyped motor behaviors were produced at either dose of SCH23390. Specifically, ANOVA revealed no significant differences among treatment groups for Locomotion [$F(2,14) = 1.84$; $P = .20$], Rearing [$F(2,14) = 0.96$; $P = .41$], or Grooming [$F(2,14) = 0.59$; $P = .59$]. Thus, as above, striatal administration of the antagonist produced a substantial, yet selective attenuation of abnormal repetitive behavior.

4. Discussion

The present study evaluated the effects of intrastriatal pharmacological manipulation on the behavior of deer mice, a rodent species that spontaneously exhibits abnormal repetitive behaviors when housed in standard laboratory cages. This is the first study to evaluate the effect of intracerebral drug administration on spontaneous and persistent stereotypy. The results indicate that spontaneously emitted jumping stereotypies can be selectively attenuated via blockade of striatal NMDA or dopaminergic D_1 receptors. The attenuation in jumping stereotypy was determined to be selective because the drug treatments administered produced statistically significant reductions in the expression of this abnormal behavior, whereas nonstereotyped motor behaviors were largely unaffected by such treatment.

The only nonstereotypic behavior altered by drug treatment was normal locomotor activity, which was significantly elevated by the higher dose of MK-801. This increased locomotor activity did not appear topographically similar to species-typical homecage locomotion, but rather took the form of thigmotaxis. Although technically speaking, this behavior could be described as patterned locomotion, we did not refer to it as such so as not to confuse it with the much more elaborate patterned running stereotypy that is spontaneously emitted by some deer mice in their home cages. This finding is consistent with previous reports of hyperlocomotion following systemic and intrastriatal administration of MK-801 in other rodent species (Al-Khatib et al., 1995; Ouagazzal et al., 1993).

The response of stereotypic colony mice to intrastriatal SCH23390 was similar to that obtained from the NMDAR antagonist, MK-801. This was expected, given the modulatory role of D_1 receptors located on striatal medium spiny neurons. When activated, these receptors enhance the responsiveness of striatal medium spiny neurons to excitatory cortical and thalamic input. Thus, blockade of striatal D_1 receptors rendered these neurons less excitable to the glutamatergic corticostriatal efferents (West and Grace, 2002), which presumably decreased activity along the implicated positive feedback circuit.

The present findings were interpreted to support the hypothesized involvement of cortico-striato-pallidonigro-thalamo-cortical feedback circuits in mediating the expression of spontaneous stereotypic behavior. Presumably, intrastriatal administration of the antagonists rendered the GABAergic medium spiny neurons less excitable, thereby reducing the inhibitory efferent activity of these neurons. This hypoactivity decreased inhibitory tone in the output nuclei of the basal ganglia, the internal globus pallidus (Gpi), and the SNpr. In response, these disinhibited GABAergic nuclei increased inhibitory tone in the excitatory Va/Vl thalamocortical relay neurons, thereby decreasing the levels of positive feedback provided to selected motor programs in the supplemental, premotor, and primary motor cortices. Thus, the decline in positive feedback to stereotypic motor programs rendered the implicated neuronal loci incapable of maintaining persistent, repetitive behaviors, and so stereotypy was attenuated. It is likely that nonstereotypic behaviors were not similarly attenuated because, at the doses used, the decrease in medium spiny neuron excitability was not sufficient to preclude the expression of discrete, purposeful movements.

The present experiment also provided important information with regard to drug-induced animal models of stereotypy. Previously cited studies have demonstrated that stereotypy can be induced pharmacologically via administration of drugs that heighten the activity of cortico-basal ganglia–cortical feedback circuits, or that such drug-induced stereotypy can be attenuated with ligands that reverse this heightened activity. Our findings indicate that, as has been determined with drug-induced models, spontaneously emitted stereotypy can be inhibited via intrastriatal administration of NMDAR or D_1R antagonists. This suggests that drug-induced stereotypy may be mediated by neuronal mecha-

nisms similar to those involved in spontaneously emitted stereotypy. This finding therefore also provides limited support to the generalizability of the results obtained from studies using drug-induced models of stereotypy.

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