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Super-Stereotypy II: Enhancement of a Complex Movement Sequence by Intraventricular Dopamine D1 Agonists

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ABSTRACT This study compared the effect of intraventricular administration of dopamine D1 or D2 agonists or of ACTH on the sequential stereotypy of a serial pattern of grooming movements ("syntactic chain"). In a previous study, we showed that peripheral administration of D1 agonists increased the probability of occurrence and enhanced the stereotypy of the already-stereotyped movement pattern. Here we made microinjections of either SKF 38393 (a partial D1 agonist; 5, 10, 15, 20, 40 μg), SKF 82958 (a full D1 agonist; 5, 10, 20 μg), quinpirole (a D2 agonist; 5, 10, 20 μg), or ACTH-(1-24) (2, 5, 10 μg) into the lateral ventricles of rats. We measured the amount of grooming, the relative probability that the complex sequence pattern would occur, and the degree to which the syntactic pattern was completed faithfully. The total amount of grooming behavior was increased by intraventricular SKF 82958 and by ACTH, but was not changed by SKF 38393 and was decreased by quinpirole. Super-stereotypy of the sequential pattern was produced only by dopamine D1 agonists. The relative probability of initiating the syntactical sequence was increased by both SKF 38393 and SKF 82958, but was reduced by quinpirole and ACTH. The full D1 agonist, SKF 82958, also increased the likelihood that the pattern would be completed, thus causing sequential super-stereotypy in the strongest sense. Our results highlight a role for dopamine D1 receptors, probably within the basal ganglia, in the production of sequential super-stereotypy of complex behavioral patterns. **Synapse 37:205–215, 2000.**

INTRODUCTION

Peripheral administration of dopamine D1 agonists elicits grooming and increases the relative probability and stereotypy of an already-stereotyped movement pattern of grooming movements, called a "syntactic chain" (Berridge and Aldridge, pages 194–204, this issue). This stereotyped movement pattern occurs naturally during grooming behavior emitted by rats, mice, and other rodents (Berridge, 1990; Berridge et al., 1987; Bolivar et al., 1996; Bursten et al., 1999). The pattern organizes dozens of forepaw stroke and licking movements into 4 sequential phases and depends on dopamine projections to the striatum (Berridge et al., 1987). The stereotyped sequence is essentially a fixed action pattern: once a normal rat has emitted the first few movements, the remaining phases will follow with 80 to 90% certainty (Berridge et al., 1987). Just as with most fixed action patterns, however, it is not 100% rigid, and that feature allows neural manipulations to produce gradations in its stereotypy.

Sequential *super-stereotypy* of syntactic grooming chains was revealed by 2 forms of pattern enhancement after D1 agonists. First, there was an increase in the relative probability that syntactic chains would be initiated during grooming, making the pattern more dominant in the overall flow of behavior. Second, the pattern itself became more sequentially stereotyped, in the sense that rats became even more likely to complete it syntactically from beginning to end. When

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given systemically, both SKF 38393, a partial dopamine D1 agonist, and SKF 82958, a full D1 agonist, produced sequential super-stereotypy in the first sense, that is, increasing the relative probability of beginning a stereotyped pattern (Berridge and Aldridge, pages 194–204, this issue). SKF 38393 also produced sequential super-stereotypy in the second sense, boosting its rate of syntactic completion to above normal levels (Berridge and Aldridge, pages 194–204, this issue). By contrast, neither a dopamine D2 agonist, quinpirole, nor the peptide, ACTH-(1-24), enhanced the pattern, and quinpirole actually reduced sequential stereotypy (Berridge and Aldridge, pages 194–204, this issue).

The relationship between excessive grooming induced by drug administration and the super-stereotypy of this movement pattern remains to be understood. Systemic SKF 38393 enhanced initiation and completion of the stereotyped pattern, but also increased the *amount* of grooming behavior as has often been reported (Deveney and Waddington, 1995, 1997; Downes and Waddington, 1993; Eilam et al., 1992; Page and Terry, 1997; Phillips et al., 1995; Starr and Starr, 1986; Trampus et al., 1993; Wachtel et al., 1992; White et al., 1988). Thus, it is conceivable that excessive grooming is always accompanied by an increase in the stereotypy of this sequential movement pattern. One of the goals of this study was to find out whether or not that is true. Another goal was to reconfirm whether D1 dopamine receptors play a special role in sequential stereotypy.

Excessive grooming is also elicited by central administration of ACTH, CRF, oxytocin, bombesin, and other peptides (Dunn, 1988; Dunn and Berridge, 1990; Dunn et al., 1987; Flynn, 1991; Gispen et al., 1975; Isaacson and Thomas, 1986; Kulkosky et al., 1988; Moody et al., 1988; Piggins and Merali, 1992; Van Erp et al., 1993). ACTH-elicited excessive grooming appears to be mediated in part by dopamine systems (Cools et al., 1978, 1988; Dunn, 1988; Guild and Dunn, 1982; Spruijt et al., 1986). ACTH causes dopamine release in the neostriatum (Florijn et al., 1993), and excessive grooming after ACTH administration is reduced by dopamine antagonist administration (Cools et al., 1987, 1988; Guild and Dunn, 1982; Isaacson et al., 1983), especially by D1 receptor antagonists (Van Wimersma Greidanus et al., 1989) or antisense (Zhang et al., 1994). Thus, the mechanism of excessive grooming elicited by ACTH appears to partly overlap with excessive grooming caused by dopamine D1 agonists.

The ability of ACTH to increase grooming behavior when administered centrally provides a means to test whether all instances of excessive grooming that involve dopamine systems necessarily also involve a concomitant increase in the strength of stereotyped sequences contained within the grooming. Or, stated conversely, it allows us to test whether the amount of grooming can be increased without increasing the relative probability or stereotypy of sequential patterns within it.

This study examines the effects of intraventricular administration of ACTH and of the dopamine D1 agonists, SKF 38393 and SKF 89528, on grooming (Berridge and Aldridge, pages 194–204, this issue).

EXPERIMENT 1
Methods

Subjects and surgery

Sprague-Dawley male rats (n = 12; 300–400 g) were housed individually on a 14/10 hour light/dark cycle throughout the experiment. All animal use procedures were approved by the University of Michigan Unit for Laboratory Animal Medicine and conformed to NIH guidelines. Each rat was surgically implanted with bilateral microinjection guide cannulae, one in the left lateral ventricle and one in the right lateral ventricle. Rats were anesthetized with ketamine (100 mg/kg, i.p.) and xylazine (10 mg/kg, i.p) and treated with atropine sulfate (3 mg/kg, i.p.) and bicillin (30,000 U i.m.). Stereotaxic coordinates for cannulae implantation were: AP = −0.8, L= ± 3.5, and V = −3.4 (each relative to bregma). Each microinjection cannulae protruded 1 mm beyond the guide cannula. After surgery, each rat received buprenorphine to alleviate discomfort during postoperative recovery (0.8 mg/kg in 3 ml saline, i.p.).

Intraventricular microinjections, drugs, and doses

Five minutes prior to each test session, rats received bilateral microinjections (3 μl) of either vehicle or drug (doses below) into the lateral ventricles. The dose was always split equally across the left and right lateral ventricles. Each rat was gently hand-held during its microinjection. The microinjection was made at a constant infusion rate over a 1-minute period. The microinjector remained in place for 30 seconds after the infusion, then the contralateral microinjection was made, the microinjector was removed, and the guide cannulae caps were replaced. The administration order of drugs, and of doses within each drug, was counterbalanced across the rats.

Experiment 1 tested the intraventricular effects of the same agents used in Experiment 1 of our peripheral administration study (Berridge and Aldridge, pages 194–204, this issue). These were SKF 38393 (a partial D1 agonist; doses = 0 [vehicle], 5.0, 10, 15, 20 μg), quinpirole (a D2 agonist; doses = 0 [vehicle], 5.0, and 10 μg), and ACTH-(1-24) (doses 0 [vehicle] 2.0, 5.0, and 10 μg). Doses were chosen from the literature on intracranial microinjection of these agents (Bordi and Meller, 1989; Cools et al., 1978; Delfs and Kelley, 1990; Dunn, 1988; Gispen and Isaacson, 1981; Isaacson and Thomas, 1986; Ranaldi and Beninger, 1994). The broadest dose range was used for SKF 38393 because

dopamine D1 receptors had been implicated in grooming stereotypy by our peripheral administration study (Berridge and Aldridge, pages 194–204, this issue), and therefore was of the greatest interest here.

Behavioral testing and video analysis

Drugs were mixed fresh daily before each test. The order of vehicle, drug, and dose administration was balanced across rats. Behavioral tests were spaced 48 hours apart. For the purpose of statistical analysis, trials in which only the control vehicle was administered were combined together for each rat to produce a single vehicle score.

All behavioral test procedures (other than the intraventricular microinjection) were identical to those used in our peripheral administration study (Berridge and Aldridge, pages 194–204, this issue). Rats were habituated to the microinjection and behavioral testing procedure for 4 consecutive days prior to the first drug administration. Each rat was placed into a chamber with a transparent floor, below which an angled mirror reflected the image of the rat's face and ventral surface into the lens of a video camera, which was able to track the movements of forepaws across the face. Videotapes were later analyzed in slow motion (frame-by-frame to 1/10th actual speed, depending on the density of movements) by trained observers who were blind to the experimental condition of each rat, for (1) grooming amount, (2) the relative probability that a syntactic chain pattern would begin during grooming, and (3) the proportion of completed syntactic chain patterns.

Grooming quantity

The quantity of grooming was measured as the number of seconds that a rat spent engaged in grooming behavior (facial strokes, paw licking, body licking), and was expressed as a percentage of the total observation session.

Probability of pattern occurrence (chain initiation)

A syntactic chain pattern contains 15–25 paw stroke and licking movements arranged into 4 consecutive phases. *Phase I:* 5 to 9 small, rapid forepaw strokes around the nose made simultaneously and symmetrically by both paws ("ellipses" because of their tight elliptical trajectories), at a rate of at least 6 Hz. *Phase II:* 1 to 4 small-to-medium strokes (up to the level of the eye) made by only one paw at a time. *Phase III:* 3 to 10 large strokes (past the ear) made simultaneously by both paws, often symmetrically. *Phase IV:* Rapid lateral turn of the head towards a flank that initiates a bout of body licking. *Initiation* of a syntactic chain was considered to be the occurrence of *Phase I followed immediately by Phase II or Phase III*. The relative probability of chain initiation was calculated for each rat as the frequency of chain initiations per minute of grooming movements (chain initiation/minute of grooming) (Berridge and Aldridge, pages 194–204, this issue). Total grooming time includes both syntactic chains and other grooming.

Pattern stereotypy (syntactic completion)

The best measure of pattern stereotypy is the probability that the pattern will be completed entirely, from Phases I to IV. A *completed pattern* was considered to be a grooming sequence in which *Phase I was followed immediately by subsequent phases leading to Phase III and then Phase IV* (Phase II is optional: most but not all syntactic grooming chains include one). Phase IV had to occur to within 5 seconds of the last Phase I stroke. The degree or quality of stereotypy was calculated as the proportion of syntactic chains that, once begun, were completed syntactically to Phase IV (Berridge and Aldridge, pages 194–204, this issue).

Histology

At the end of the experiment, rats were deeply anesthetized with sodium pentobarbital. In order to confirm correct placement of the cannulae, 3 μl of ink was injected into each side of the lateral ventricles. The rats were perfused intracardially with saline, and the brains were removed and inspected for the presence of ink within both lateral ventricles.

Results

Grooming amount

The amount of time rats spent in grooming was significantly altered by intraventricular drug administration ($F(2,143) = 13.81$, $P < 0.01$; 2-way repeated-measures ANOVA, where drug type and dose were the main factors; Fig. 1). Intraventricular ACTH microinjections increased the amount of grooming in proportion to dose, more than doubling grooming amount at the highest ACTH dose, which is consistent with many earlier reports ($F(3,47) = 36.92$, $P < 0.01$). Intraventricular SKF 38393 microinjections did not change the amount of grooming from vehicle control levels ($F(4,59) = 2.14$, n.s.). Quinpirole dramatically reduced the proportion of time spent grooming at both doses ($F(2,35) = 17.2$, $P < 0.01$).

Initiation of syntactic chain sequences

The relative probability of beginning the sequential pattern was altered by drug administration ($F(2, 143) = 17.2$, $P < 0.01$; Fig. 2). The tendency to initiate a syntactic chain pattern was increased only by SKF 38393, which at the highest doses nearly doubled the relative probability of beginning a chain pattern during grooming bouts ($F(4,59) = 11.4$, $P < 0.01$). By contrast, ACTH microinjections suppressed the relative probability of beginning the stereotyped pattern, especially

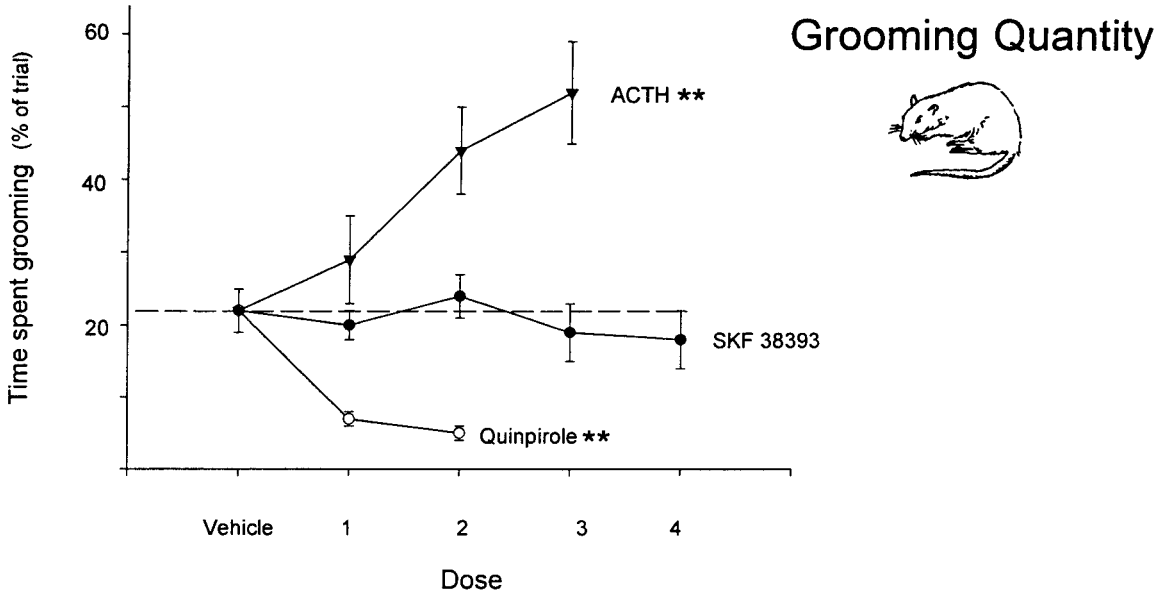

Fig. 1. Grooming amount (Experiment 1). Effects on time spent grooming of intraventricular SKF 38393, quinpirole, and ACTH. Amount of grooming is expressed as the percentage of time spent grooming out of the entire observation period (symbolized by rat engaged in grooming behavior). Dose 1: SKF 38393 = 5.0 μg, quinpirole = 5.0 μg, and ACTH-(1-24) = 2.0 μg. Dose 2: SKF 38393 = 10 μg, quinpirole = 10 μg, and ACTH = 5.0. μg. Dose 3: SKF 38393 =15 μg, and ACTH 10μg. Dose 4: SKF 38393 = 20 μg. An asterisk denotes a change from baseline level produced by a compound, statistically significant at $P < 0.05$. Two asterisks denote a change from baseline significant at $P < 0.01$.

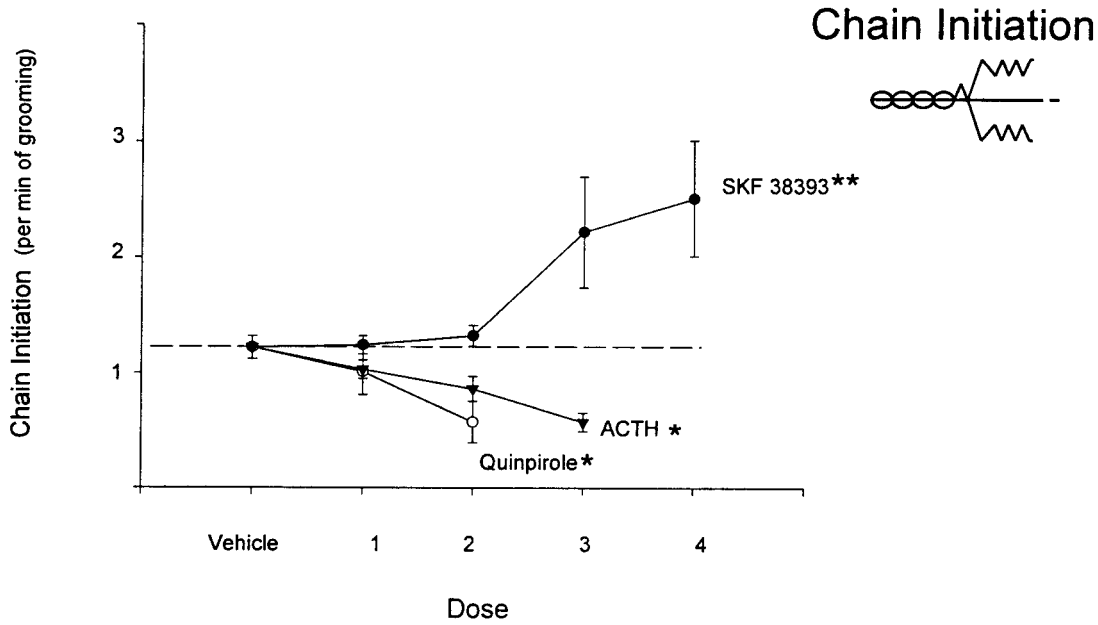

Fig. 2. Pattern probability: syntactic chain initiation (Experiment 1). Effects on the relative probability of beginning a stereotyped pattern of intraventricular SKF 38393, quinpirole, and ACTH. Relative probability is expressed as the rate of initiation of syntactic chains per minute of grooming behavior (symbolized by choreograph of first 3 phases of a syntactic grooming chain). Dose 1: SKF 38393 = 5.0 μg, quinpirole = 5.0 μg, and ACTH-(1-24) = 2.0 μg. Dose 2: SKF 38393 = 10 μg, quinpirole = 10 μg, and ACTH = 5.0. μg. Dose 3: SKF 38393 =15 μg, and ACTH 10μg. Dose 4: SKF 38393 = 20 μg. Statistical symbols as in Figure 1.

at higher doses ($F(3,47) = 7.5$, $P < 0.05$), even though those had promoted the total amount of grooming. Quinpirole microinjections also significantly suppressed the initiation of syntactic chains in proportion to dose ($F(2,35) = 6.48$, $P < 0.05$).

Pattern stereotypy: syntactic completion

The likelihood of completing the movement pattern in a fully stereotyped fashion, from Phase I through Phase IV, was altered by drug administration (F2, 143) = 15.73,

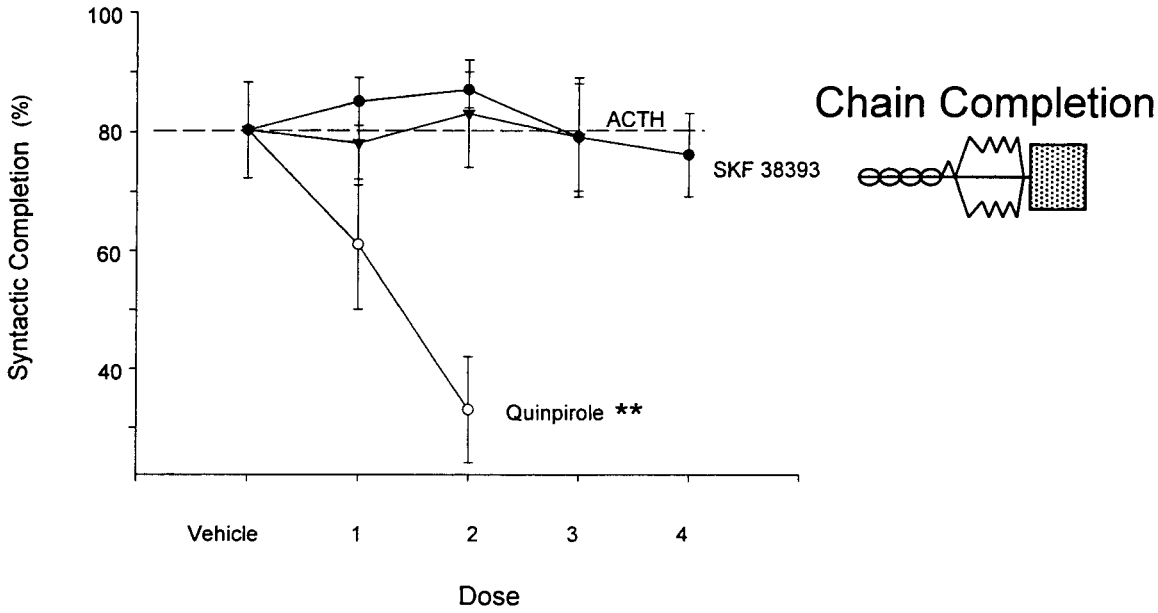

Fig. 3. Pattern stereotypy: syntactic chain completion (Experiment 1). Effects on the completion of syntactic chain patterns of intraventricular SKF 38393, quinpirole, and ACTH. Syntactic completion is expressed as the percentage of grooming chains that were fully completed through Phase IV, as a proportion of those that were begun (symbolized by choreograph of completed syntactic grooming chain). Dose 1: SKF 38393 = 5.0 μg, quinpirole = 5.0 μg, and ACTH-(1-24) = 2.0 μg. Dose 2: SKF 38393 = 10 μg, quinpirole = 10 μg, and ACTH = 5.0. μg. Dose 3: SKF 38393 =15 μg, and ACTH 10μg. Dose 4: SKF 38393 = 20 μg. Statistical symbols as in Figure 1.

$P < 0.01$; Fig. 3). After vehicle microinjections, rats completed approximately 80% of their stereotyped chain patterns all the way to Phase IV (80.2 ± 8%). This baseline proportion of completed sequences was slightly lower than found in most other studies (85 to 90%), perhaps because of effects of the microinjection handling procedure or because of the presence of the guide cannula implant on the skull, which might have disrupted grooming sequences. Neither SKF 38393 microinjections ($F(4,59) = 0.72$, n.s.) nor ACTH microinjections ($F(3,47) = 0.97$, n.s.) significantly altered the stereotypy of this pattern in terms of the proportion of sequences completed. However, quinpirole microinjections produced a dramatic suppression of stereotypy, reducing the proportion of syntactic chains that were completed in a stereotyped fashion to below one-half of the baseline levels at the highest dose ($F(2,35 = 21.8$, $P < 0.01$).

Discussion of experiment 1

ACTH elicited excessive grooming as expected when administered intraventricularly. However, ACTH-induced excessive grooming was not accompanied by an increase in the relative probability or the pattern stereotypy of the syntactic grooming sequence. On the contrary, intraventricular ACTH diminished the relative probability of beginning the syntactic chain pattern, and had no effect on the completion levels or stereotypy of patterns that were begun. This indicates that excessive grooming evoked by neuropharmacological manipulations need not necessarily be accompanied by enhancement of stereotyped sequential patterns contained within the grooming.

Quinpirole, the dopamine D2 agonist, suppressed all aspects of grooming. The amount of grooming, the relative probability of initiating a syntactic chain pattern during the grooming that remained, and the likelihood of completing the pattern in a stereotyped way if it began, all were diminished after the D2 agonist. Each of these effects were similar to those of peripheral administration of quinpirole (Berridge and Aldridge, pages 194–204, this issue).

Interestingly, intraventricular SKF 38393, the D1 agonist, increased the relative probability of beginning a stereotyped sequential pattern, as it does when delivered peripherally (Berridge and Aldridge, pages 194–204, this issue). However, it left unchanged the 80% proportion of stereotyped chains that were completed syntactically all the way to Phase IV, although when given peripherally in our earlier study it also increased completion stereotypy (Berridge and Aldridge, pages 194–204, this issue). Further, although SKF 38393 increased the probability of syntactic chain patterns, it did not increase the total amount of grooming movements at any of the doses tested. Taken together with the effect of ACTH, which increased the amount of grooming without increasing completion stereotypy, this represents a double dissociation between the *amount of grooming movements* vs. the *relative probability of stereotyped movement patterns* during grooming.

It seemed possible that the doses of SKF 38393 used in Experiment 1 were too low to increase grooming, since they overlap with doses that have been microinjected directly into brain structures such as the neo-

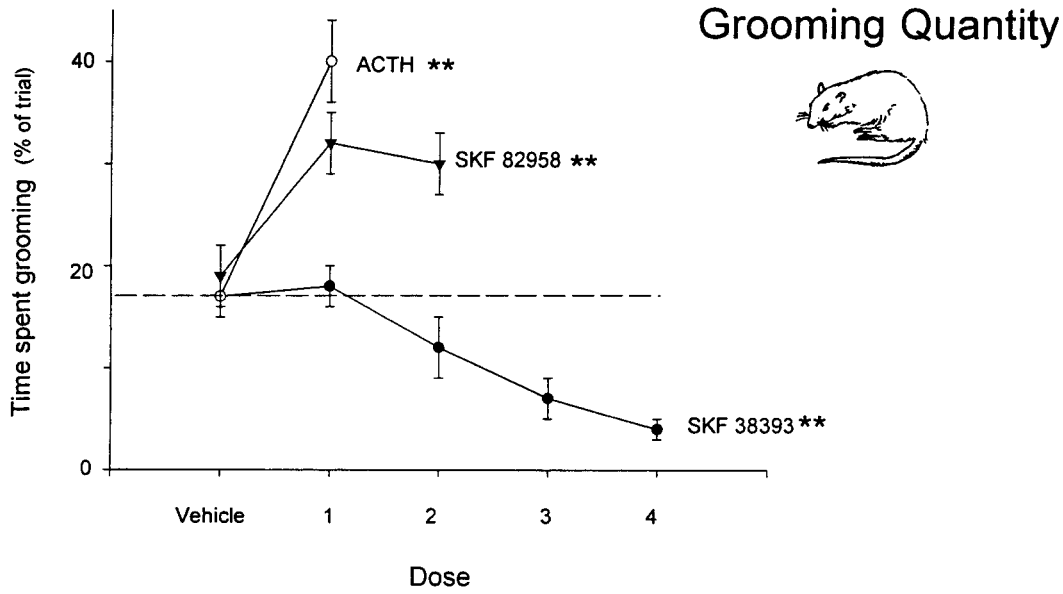

Fig. 4. Grooming amount (Experiment 2). Effects on time spent grooming of intraventricular SKF 38393, quinpirole, and ACTH. Amount of grooming is expressed as the percentage of time spent grooming out of the entire observation period (symbolized by rat engaged in grooming behavior). Dose 1: SKF 38393 = 10 μg, SKF 82958 = 5.0 μg, and ACTH-(1-24) = 10 μg. Dose 2: SKF 38393 = 20 μg, and SKF 82958= 10 μg. Dose 3: SKF 38393 =40 μg, and Dose 4: SKF 38393 = 80 μg. Statistical symbols as in Figure 1.

striatum (Bordi and Meller, 1989; Delfs and Kelley, 1990; Ranaldi and Beninger, 1994). In order to test the effects of higher doses, Experiment 2 re-examined the effects of SKF 38393 on grooming amount and stereotypy using doses between 10–80 μg. ACTH was also included in Experiment 2 at the dose that had most effectively increased grooming amount in Experiment 1 (10 μg), in order to replicate whether ACTH-induced excessive grooming occurs without increases in pattern stereotypy. Finally, we compared the intraventricular effects of SKF 82958, a full D1 agonist, which we previously had found to enhance pattern initiation when given systemically (Berridge and Aldridge, pages 194–204, this issue).

EXPERIMENT 2

Methods

Subjects and compounds

Naive Sprague-Dawley male rats (n = 24; 300–400 g) were implanted with bilateral microinjection cannulae in the lateral ventricles, and were tested using the same procedure as in Experiment 1. Drugs and doses were: SKF 38393 (0 [vehicle], 10, 20, 40, and 80 μg, i.c.v.); ACTH-(1-24): (0 [vehicle], and 10 μg, i.c.v.); SKF 82958: 0 μg (vehicle), 5.0 and 10 μg (each dose split between the two lateral ventricles). Twelve rats received all doses of SKF 38393 and of ACTH, and 12 rats received all doses of SKF 82958, in counter-balanced order.

Results

Amount of grooming

ACTH again increased the amount of grooming to more than 200% the vehicle control level ($F(5,71) = 22.7$, $P < 0.01$; post hoc paired-comparison tests of ACTH to vehicle, Bonferroni $P < 0.05$, Fig. 4). By contrast, SKF 38393 microinjections reduced the proportion of time spent grooming, roughly in proportion to dose ($F(4, 59) = 18.6$, $P < 0.01$). At the 80-μg dose, the highest dose tested, the amount of grooming was only 25% of the vehicle control level ($P < 0.05$, Bonferroni). SKF 82958, the full D1 agonist, significantly *increased* the amount of time rats spent in grooming ($F(2,35) = 6.67$, $P < 0.01$). The amount of grooming was raised after SKF 82958 to approximately 150% of the vehicle control level by both the 5 μg dose and the 10 μg dose (each dose compared to control level, $P < 0.05$, Bonferroni).

Initiation of syntactic chain sequence pattern

SKF 38393 again increased the probability of beginning a stereotyped movement pattern in a dose-dependent fashion ($F(4,59) = 5.52$, $P < 0.01$; Fig. 5). SKF 82958 also increased the relative probability of initiating a syntactic chain pattern ($F(2,35) = 15.92$, $P < 0.001$), just as SKF 38393 did. At the 80-μg dose of SKF 38393, and at the 5- and 10-μg doses of SKF 89528, the relative probability of initiating a chain was more than 200% of the vehicle control level ($P < 0.05$ each, Bonferroni). By contrast, ACTH again reduced the tendency to initiate the stereotyped movement pattern ($P < 0.05$, Bonferroni).

Pattern stereotypy: syntactic completion

On vehicle control trials, rats in this experiment completed approximately 70% of their syntactic chains

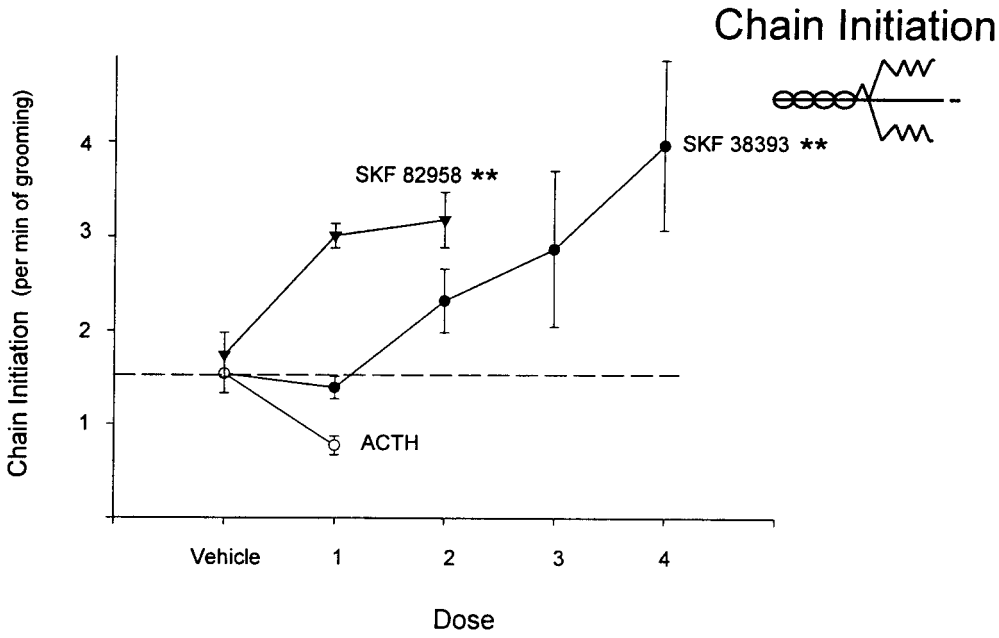

Fig. 5. Pattern probability: syntactic chain initiation (Experiment 2). Effects on the relative probability of beginning a stereotyped pattern of intraventricular SKF 38393, quinpirole, and ACTH. Relative probability is expressed as the rate of initiation of syntactic chains per minute of grooming behavior (symbolized by choreograph of first 3 phases of a syntactic grooming chain). Dose 1: SKF 38393 = 10 μg, SKF 82958 = 5.0 μg, and ACTH-(1-24) = 10 μg. Dose 2: SKF 38393 = 20 μg, and SKF 82958= 10 μg. Dose 3: SKF 38393 =40 μg, and Dose 4: SKF 38393 = 80 μg. Statistical symbols as in Figure 1.

to Phase IV (Fig. 6). This again is a lower baseline level of stereotypy than seen in most earlier studies, and may be related to the intraventricular administration procedure or the presence of cannulae implants on the head. ACTH did not alter this control level of stereotypy, just as it failed to do so in Experiment 1. SKF 38393, at the lower doses (used also in Experiment 1), also did not alter the level of pattern stereotypy. SKF 38393 at the highest two doses actually suppressed pattern completion to about one-half the vehicle control level ($(F(5,71) = 7.01, P < 0.01$; $P < 0.05$ each for the 2 highest doses, Bonferroni).

By contrast, SKF 82959, the full D1 agonist, enhanced syntactic completion or sequential stereotypy of the pattern ($F(2,35) = 4.23, P < 0.05$). The proportion of completely stereotyped patterns rose from about 70 to 84% of syntactic chains after 5 μg SKF 82958, and to 86% after 10 μg SKF 82958 ($P < 0.05$, Bonferroni).

GENERAL DISCUSSION

The results of these intraventricular microinjection experiments confirm that dopamine D1 receptors play a special role in controlling the stereotypy of a complex sequential pattern of movements. Both SKF 38393 and SKF 82958 increased the relative probability that the syntactic grooming chain would begin during a grooming bout. Additionally, the full D1 agonist SKF 82958 produced sequential super-stereotypy of the pattern itself, making rats even more likely than normal to complete all 4 phases in syntactic order.

Neither quinpirole, a D2 dopamine agonist, nor ACTH-(-24) increased the relative probability or the stereotypy of the movement pattern, even though ACTH (like SKF 82958) produced excessive grooming. Both quinpirole and ACTH instead suppressed the relative probability of beginning the complex stereotyped movement pattern, and either suppressed or had no effect on pattern stereotypy or completion. These results clearly indicate that control of the *amount of grooming* behavior can be decoupled from control of *stereotypy of sequential patterns* within grooming. Intraventricular ACTH increased grooming movements, but decreased the probability of engaging in a syntactic chain pattern, whereas SKF 38393 increased the probability of the stereotyped movement pattern, but decreased the amount of grooming movements. This double dissociation demonstrates that sequential stereotypy is not a necessary concomitant of excessive grooming.

Comparison to peripheral administration: amount of grooming

ACTH is well known to produce excessive grooming only when it is given centrally, and not when given peripherally (Dunn, 1988; Gispen and Isaacson, 1981). However, the opposite now appears to be true for SKF 38393. Peripheral administration of that partial D1 agonist robustly increases grooming amount (Fletcher and Starr, 1987; Page and Terry, 1997; Starr and Starr, 1986; White et al., 1988), and also increases completion of the stereotyped movement pattern (Berridge and Aldridge, pages 194–204, this issue). Our

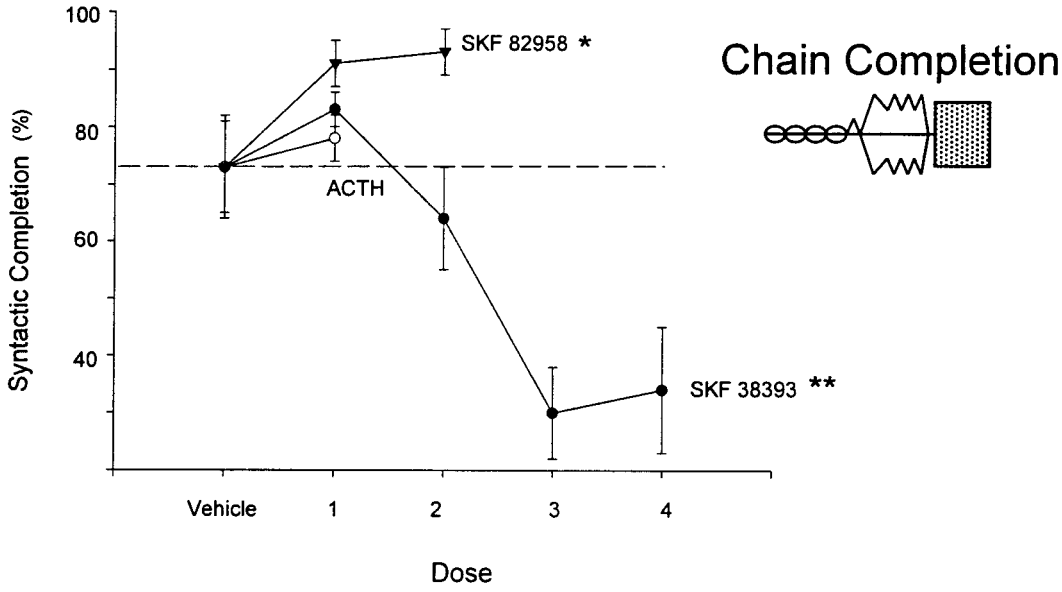

Fig. 6. Pattern stereotypy: syntactic chain completion (Experiment 2). Effects on the completion of syntactic chain patterns of intraventricular SKF 38393, quinpirole, and ACTH. Syntactic completion is expressed as the percentage of grooming chains that were fully completed through Phase IV, as a proportion of those that were begun (symbolized by choreograph of completed syntactic grooming chain). Dose 1: SKF 38393 = 10 μg, SKF 82958 = 5.0 μg, and ACTH-(1-24) = 10 μg. Dose 2: SKF 38393 = 20 μg, and SKF 82958 = 10 μg. Dose 3: SKF 38393 =40 μg, and Dose 4: SKF 38393 = 80 μg. Statistical symbols as in Figure 1.

present results indicate that SKF 38393 fails to produce excessive grooming when it is administered intraventricularly. We note there are a few reports of increased grooming produced by central administration of SKF 38393 (Fletcher and Starr, 1987; Hartgraves and Randall, 1986). However, those studies have generally described animals that received 6-hydroxydopamine lesions prior to receiving the drug, which would result in dopamine-denervation and receptor supersensitivity (Fletcher and Starr, 1987; Hartgraves and Randall, 1986). Prior dopamine lesions may be needed for the elicitation of excessive grooming by central SKF 38393. To our knowledge, excessive grooming elicited by central administration of SKF 38393 has not been reported in normal rats (Bordi and Meller, 1989; Phillips et al., 1995), so our finding that intraventricular SKF 38393 fails to promote the amount of grooming (and actually suppresses grooming at high doses) may not contradict published results.

By contrast, SKF 82958, a full D1 agonist, did produce excessive grooming after intraventricular administration in normal rats. We believe this may be the first report of excessive grooming induced by central administration of a D1 dopamine agonist in normal animals. Interestingly, SKF 82958 did not produce excessive grooming after systemic administration in a companion study (Berridge and Aldridge, pages 194–204, this issue), providing another central vs. peripheral difference.

It is not clear why the amount of grooming should be affected differently by a D1 dopamine agonist after central vs. peripheral administration. One possible factor that could influence the differences between central vs. peripheral administration may be differential diffusion to the diverse brain regions relevant to these behavioral effects. For example, the relative distribution of the drug between ventral and dorsal striatum might be important to the effects on grooming amount and stereotypy (Cromwell and Berridge, 1996; Dickson et al., 1994; Fletcher and Starr, 1987; Neisewander et al., 1995). Peripheral agents must reach targets through the blood supply, receiving general distribution across neuroanatomical sites. Micro-injection into the cerebral ventricles, by comparison, provides intense and direct stimulation of structures adjacent to the ventricles, but relatively less stimulation to more distal structures. Another factor might be interaction between D1 and D2 families of receptor subtypes. Each drug produces a different pattern of activation across these subtypes. SKF 38393 is only a partial D1 agonist, achieving less adenylate cyclase activity than dopamine itself, whereas SKF 82958 is a full D1 agonist (Mottola et al., 1996). In addition, SKF 82958 has been suggested to have effects on D2 autoreceptors (Ruskin et al., 1998). Although D2 receptor activation by quinpirole does not enhance grooming, there have been suggestions that the effects of D2 receptor activation may be gated by simultaneous D1 activation (Bordi and Meller, 1989; Wachtel et al., 1989; White et al., 1988; Wirtshafter and Krebs, 1997), and the possibility of receptor subtype interaction regarding grooming deserves exploration.

Comparison to peripheral administration: sequential stereotypy of grooming

The sequential stereotypy of grooming has now been demonstrated to be enhanced by both peripheral and intra-ventricular administration of D1 agonists. The relative probability of initiating a syntactic grooming chain pattern was always enhanced by D1 agonist administration, regardless of whether of SKF 38393 or SKF 89258 was given, and regardless of whether the route of administration was central or peripheral (Berridge and Aldridge, pages 194–204, this issue). Super-stereotypy of pattern completion, however, depended on the route of administration. In this study, super-stereotypy of pattern completion was produced only by intraventricular SKF 82958. By contrast, only SKF 38393 produced super-stereotypy of pattern completion after peripheral administration. The same interactions involving differential diffusion to neuroanatomical targets, or degree of D1 vs. D2 receptor subtype activation, that are relevant to excessive grooming may also apply to the effect of route of administration on stereotypy of syntactic pattern completion.

Role of neostriatum and mesostriatal dopamine projections in pattern stereotypy

Relevant to our conclusion that D1 dopamine receptors mediate sequential super-stereotypy, a previous study found that mutant mice lacking dopamine D1-A receptors have *deficits* in the stereotypy of their syntactic chains of grooming movements (Cromwell et al., 1998). The stereotyped pattern of syntactic grooming chains is also disrupted in mice by the Weaver gene mutation that alters the nigrostriatal dopamine system (Bolivar et al., 1996; Coscia and Fentress, 1993), and is disrupted in rats by 6-OHDA lesions of the substantia nigra in rats, which destroy dopamine projections to the neostriatum (Berridge, 1989), as well as by excitotoxin lesions or ablation of the neostriatum itself (Berridge and Fentress, 1987; Berridge and Whishaw, 1992; Cromwell and Berridge, 1996). Thus, the nigrostriatal system appears to be crucial to control this sequential pattern.

Electrophysiological studies by Aldridge and colleagues have identified a neuronal basis in the neostriatum that may mediate this stereotyped movement pattern (Aldridge and Berridge, 1998; Aldridge et al., 1993). In one study, approximately 40% of neostriatal neurons coded a sequential aspect of the movement pattern, compared to only 14% that coded motor aspects of component movements (Aldridge and Berridge, 1998). Neurons that responded to sequential aspects of the stereotyped movement pattern were distributed anatomically throughout the neostriatum, but coding of the pattern appeared to be especially strong for neurons in the anterior dorsolateral region of the neostriatum. In the dorsolateral neostriatum, neurons increased activity by over 100% during this stereotyped movement pattern, compared to only 30% by neostriatal neurons elsewhere (Aldridge and Berridge, 1998). In addition, dorsolateral neostriatal neurons were more likely than other neurons to code multiple sequential phases of the pattern most relevant to completion or pattern stereotypy (since terminal phases are what completed patterns have, and what incomplete patterns lack) (Aldridge and Berridge, 1998). The hypothesis that the sequential stereotypy of behavior might be mediated by particular neostriatal neurons is compatible with recent computer models suggesting that the sequencing of behavior might be controlled as a specific function by a dedicated population of basal ganglia neurons (Berns and Sejnowski, 1998).

Clinical implications

Super-stereotypy of complex behavioral sequences is a feature of several human disorders, such as Tourette's syndrome and obsessive-compulsive disorder (Rapoport and Wise, 1988; Toates, 1990). It is widely believed that mesostriatal dopamine systems may be involved in the generation of these complex stereotypies of movement and thought (Goodman et al., 1990; Hollander et al., 1989; McDougle, 1997; Rapoport, 1994; Ridley, 1994). Specifically, hyperactivity in dopamine systems (coupled with dysfunction of serotonin systems) has been suggested by many investigators to be involved in stereotypy disorders, based on the logic that dopamine antagonists (combined with other agents) are helpful in treating the stereotypies of some patients (Goodman et al., 1990; McDougle, 1997; McDougle et al., 1993). Other evidence comes from observations of the induction of human stereotypies by drugs that promote dopamine neurotransmission. For example, cocaine has been reported to worsen the symptoms of Tourette's syndrome (Cardoso and Jankovic, 1993). Similarly, the removal of long-term clozapine treatment, after dopamine receptor upregulation, results in tics and in obsessive-compulsive symptoms in some patients (Poyurovksy et al., 1998). However, the role of particular dopamine receptor subtypes remains unclear in the behavioral stereotypies of Tourette's or obsessive-compulsive disorder. Although a link to D_2 receptors has been suggested for such disorders (Comings et al., 1991), other studies have rejected such a link (Gelernter et al., 1990, 1994). Negative results have similarly been reported for links between obsessive-compulsive disorder or Tourette's syndrome and the specific dopamine D_3 receptor (Catalano et al., 1994), D_4 receptor (Barr et al., 1996), and D_5 receptor subtypes (Barr et al., 1997). Negative results of a few studies do not conclusively rule out a role for these receptor subtypes, of course, but they indicate that the relation of pathological sequential stereotypy to a receptor subtype remains opaque.

Our own results suggest the possibility of a special role for the D1 family of dopamine receptor subtypes

since only the D1 agonists, SKF 38393 and SKF 89258, produced super-stereotypy of the complex movement pattern studied here after intraventricular or peripheral administration (Berridge and Aldridge, pages 194–204, this issue). Still, it must be acknowledged that the role of D1 receptors in human clinical conditions is no more clear than the others. For example, SKF 38393 has been reported not to worsen the symptoms of Tourette's syndrome (Braun et al., 1989). But Tourette's patients may contain multiple subgroups of individuals who respond differently to drug administration (Petter et al., 1998). The role of D1 activation in human patients with sequential super-stereotypy may be worth closer examination.

Conclusion

The results of these experiments, and of our companion study (Berridge and Aldridge, pages 194–204, this issue), indicate a special role for central dopamine D1 receptors in the sequential stereotypy of behavior. Only D1 agonists appear to produce super-stereotypy of the sequential pattern of syntactic grooming chains. Neither a D2 agonist nor ACTH increased stereotypy of the pattern, regardless of whether they increased grooming movements. Our results thus highlight a potential role for D1 dopamine receptors, probably within the basal ganglia, in the production of sequential super-stereotypy of complex behavioral patterns.

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