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Tolerance to the disruptive effects of Δ^9-THC on learning in rats

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Abstract

Tolerance to the effects of the cannabinoid agonist Δ^9-tetrahydrocannabinol (Δ^9-THC) was characterized in rats responding under a multiple schedule of repeated acquisition and performance. During the acquisition component, subjects acquired a different three-response sequence each session, whereas in the performance component the sequence was the same each session. Responding was maintained under a second-order fixed-ratio 2 (FR2) schedule of food reinforcement. Acute doses of Δ^9-THC (1–10 mg/kg) decreased rate and accuracy in both components, whereas doses of the cannabinoid (CB1) receptor antagonist *N*-(piperidin-1-yn-)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride (SR141716A; 0.32 and 1 mg/kg) were ineffective. While 5.6 mg/kg of Δ^9-THC disrupted responding when administered acutely, tolerance to the rate-decreasing and error-increasing effects of this dose developed in both components after daily administration. When 1 mg/kg of SR141716A was substituted for Δ^9-THC during chronic administration, this previously ineffective dose selectively increased within-session errors in the acquisition component of the multiple schedule. During the postchronic phase, subjects were generally less sensitive to the disruptive effects of Δ^9-THC. In summary, these data demonstrated that tolerance to Δ^9-THC developed across two different behavioral tasks and that learning was generally more sensitive than performance to the effects of SR141716A during chronic treatment with Δ^9-THC.

Keywords: Δ^9-THC; SR141716A; Naltrexone; Long–Evans rats; Repeated acquisition; Learning; Tolerance; Dependence

1. Introduction

In addition to producing antinociception and hypothermia in various species (Dewey, 1986; Hollister, 1986), acute administration of Δ^9-tetrahydrocannabinol (Δ^9-THC) produces dose-related disruptions in the acquisition of complex operant tasks (Branch et al., 1980; Brodkin and Moerschbaecher, 1997; Nakamura-Palacios et al., 2000; Winsauer et al., 1999a) and the retention of complex discriminations (Aigner, 1988; Lichtman et al., 1995; Zimmerberg et al., 1971). For example, Nakamura-Palacios et al. (2000) demonstrated that the acute administration of Δ^9-THC to squirrel monkeys decreased both the overall rate and accuracy of learning under a repeated-acquisition task. Similarly, Kamien et al. (1994) demonstrated that orally administered Δ^9-THC produced selective disruptions in the acquisition of response sequences in humans responding under a multiple schedule of repeated acquisition and performance. These data indicated that the acute administration of Δ^9-THC can produce dose-related disruptions in the acquisition of complex discriminations in a variety of species responding under similar repeated-acquisition tasks.

Many of the effects produced by Δ^9-THC are reduced during chronic administration (i.e., tolerance develops; Branch et al., 1980; Ferraro and Grilly, 1974; Ferraro and Grisham, 1972; Jones et al., 1981; Pertwee et al., 1993). For example, Branch et al. (1980) reported that tolerance developed to both the rate- and accuracy-decreasing effects of Δ^9-THC in squirrel monkeys responding under either a two- or five-key behavioral task. These investigators found that the level of tolerance that developed under the five-key task was not as complete as the level of tolerance that developed under the two-key task. Ferraro and Grilly (1974) also reported that tolerance developed to the effects of Δ^9-THC after it was administered chronically for a 5-month

Abbreviations: Δ^9-THC, Δ^9-tetrahydrocannabinol; SR141716A, *N*-(piperidin-1-yn-)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride.

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period in nonhuman primates responding under a delayed matching-to-sample task. In that study, tolerance to the disruptive effects of Δ^9-THC developed in subjects who had a history of chronic administration of the drug, and not in subjects who were drug naïve. Together, these studies demonstrated how the development of tolerance could be readily influenced by variables such as task complexity and drug history.

Dependence can also develop during the chronic administration of Δ^9-THC (Aceto et al., 1996; Beardsley et al., 1986; Beardsley and Martin, 2000; Fredericks and Benowitz, 1980; Haney et al., 1999; Hutcheson et al., 1998; Jones et al., 1981) . Physical dependence has been demonstrated by the presence of a withdrawal syndrome in various species after chronic administration of Δ^9-THC is suspended (i.e., spontaneous withdrawal) or after an antagonist is administered (i.e., precipitated withdrawal). Jones et al. (1981) reported that a withdrawal syndrome occurred in humans when the chronic administration of Δ^9-THC was temporarily suspended. This syndrome was characterized by restlessness, irritability and insomnia. In rats, Aceto et al. (1996) demonstrated that there was a significantly greater number of withdrawal signs exhibited in Δ^9-THC-treated subjects than in saline-treated subjects when challenged with the cannabinoid receptor antagonist *N*-(piperidin-1-yn-)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride (SR141716A). Besides overt signs of withdrawal, dependence has also been demonstrated by changes in operant responding. For example, Beardsley and Martin (2000) have demonstrated the development of dependence in rats chronically treated with Δ^9-THC, as indicated by the decrease in response rate when withdrawal was precipitated with the administration of SR141716A. Data from these studies on dependence have indicated that the chronic administration of Δ^9-THC can produce physiological and behavioral changes in both humans and rats, which become apparent when withdrawal is either spontaneous or precipitated.

Whereas the behavioral studies mentioned above have provided insights into the pharmacology of cannabinoids under both acute and chronic conditions, there are still questions about how complex processes such as learning might be affected by tolerance to and dependence on Δ^9-THC. For example, chronic studies with cannabinoids are needed to examine whether the quality of responding (i.e., accuracy) can be affected independently of the quantity of responding (i.e., response rate), and to determine the degree to which each of these measures of behavior are affected by spontaneous or precipitated withdrawal. In order to extend the previously mentioned findings with Δ^9-THC, the present study examined the effects of chronic administration of Δ^9-THC, and the effects of the cannabinoid antagonist SR141716A, during chronic treatment in subjects responding under a multiple schedule of repeated acquisition and performance. Specifically, these experiments were conducted in order to examine whether tolerance develops equally across two different behavioral tasks, and whether responding in each task was differentially sensitive to the disruptive effects of an antagonist during chronic treatment with Δ^9-THC.

2. Methods

2.1. Subjects

Four naive male Long–Evans rats maintained at 80% of their free-feeding weight served as subjects. These body weights, which were maintained throughout the experiment, ranged from 290 to 385 g with a mean body weight of 335 g. Food was earned during the experimental session and, if necessary, was provided after the session to maintain the subjects at the specified body weight. Water was always available in the home cage. All subjects were housed individually in plastic cages containing sterilized hardwood-chip bedding. The housing room was maintained at 21 ± 1 °C with 50 ± 10% relative humidity on a 12-h light/dark cycle, which began at 7 a.m. each day. In all situations, the ''Principles of Laboratory Animal Care'' (NIH publication No. 85-23, revised 1985) were followed in conducting these experiments.

2.2. Apparatus

Four identical modular chambers (model E10-10TC; Coulbourn Instruments, Lehigh Valley, PA) configured specifically for rodents were used. The front wall of each chamber contained a house light, auditory feedback relay, pellet trough (2 cm above the floor and centered), and three response keys aligned horizontally (8 cm apart, center to center, and 11.5 cm above the floor). Each response key could be transilluminated by three Sylvania 28ESB-indicator lamps, one with a red plastic cap, one with a yellow plastic cap and one without a colored plastic cap (white). Response keys required a minimum force of 0.15 N for activation, and correct responses on each key produced an audible click of the feedback relay. Each chamber was enclosed within a sound-attenuating cubicle equipped with a fan for ventilation and for masking extraneous noises. The chambers were connected to a computer (HD Personal Computer 486-DX 66) programmed in MED-PC/MED-STATE NOTATION software (MED Associates and Thomas Tatham, St. Albans, VT) and to cumulative recorders (Gerbrands, Arlington, MA) located within the room.

2.3. Procedure

Preliminary training of the subjects was similar to that described for rats by Winsauer et al. (1999b) and included magazine training, shaping of the response (nose press), and reinforcing responses on each of the three keys after shaping. When subjects demonstrated stable responding

under a one-response discrimination task, another response (associated with a different colored stimulus) was added until each subject was able to respond on a three-response sequence. The terminal baseline was a multiple schedule with repeated-acquisition and performance components.

During experimental sessions, all three response keys were illuminated at the same time with one of three colors, either white, red or yellow. The subject's task was to respond on the correct key in the presence of each sequentially illuminated set of colors (e.g., keys white, center correct; keys red, left correct; keys yellow, right correct). Completion of this sequence turned off the key lights, reset the sequence and produced a 0.5-s flash of the feeder light in the food trough. The same sequence (in this case, center–left–right or C–L–R) was repeated throughout a given session and responding on this sequence was maintained by food presentation under a second-order fixed-ratio 2 schedule (FR2); i.e., every second completion of the sequence produced a food pellet. When the subject pressed an incorrect key (in the example, the left or right key when the white key lights were illuminated), the error was followed by a 5-s timeout. During a timeout, the keylights were turned off and responses had no programmed consequence. An incorrect response did not reset the three-response sequence; that is, the stimuli were the same before and after a timeout.

To establish a steady state of repeated acquisition, the three-response sequence was changed from session to session. An example of a typical set of five sequences (for five different sessions) was as follows: C–L–R, L–R–C, C–R–L, R–L–C, and L–C–R, with the order of the color presentations always white, red, and yellow. The sequences were carefully selected to be equivalent in several ways and there were restrictions on their ordering across sessions. More specifically, each sequence was scheduled with equal frequency and adjacent positions within a sequence for a given session were different. Occasionally, a correct sequence position for a given color was the same for two consecutive sessions (as in the above list of sequences, L–R–C and C–R–L).

During the performance component of the multiple schedule, the response keys and the house light above the keys were illuminated. In this component, the three-response sequence remained the same (R–C–L) from session to session. Note that subjects responded on this sequence in the performance component only. In all other aspects (colored stimuli for each response in the three-response sequence, FR2 schedule of food presentation, timeout duration of 5 s, etc.), the performance component was identical to the acquisition component.

Experimental sessions began with an acquisition component, which then alternated with a performance component after 40 reinforcers or 20 min, whichever occurred first. Each session was terminated after 200 reinforcers or 100 min, whichever occurred first. When response rate or percentage of errors no longer showed systematic change from component to component or session to session (i.e., each subject developed a steady state of repeated acquisition and responding in the performance component was stable), drug testing began. The study consisted of three phases that occurred in the following order: an acute phase, a chronic phase, and a postchronic phase. Dose–effect curves for Δ^9-THC (1 to 10 mg/kg), as well as two doses of SR141716A (0.32 and 1 mg/kg) and naltrexone (0.32 and 1 mg/kg), were determined in the acute phase. During the chronic phase, 5.6 mg/kg of Δ^9-THC was administered 30 min before the start of each session. When a subject's behavior returned to control levels or 30 days had elapsed, whichever occurred first, 1 mg/kg of SR141716A was substituted for the subject's daily dose of Δ^9-THC on two or more occasions. Subsequently, 1 mg/kg of naltrexone was also substituted for Δ^9-THC. Δ^9-THC was always administered the day following substitution with either SR141716A or naltrexone. To determine if the temporary suspension of chronic Δ^9-THC alone would disrupt responding, three of the four subjects did not receive their daily dose of Δ^9-THC before an experimental session. After the termination of chronic Δ^9-THC, saline was administered to all of the subjects for 15 consecutive days. Seven to twelve weeks after saline was administered, dose–effect curves for Δ^9-THC were redetermined for each subject.

2.4. Drugs

Δ^9-THC, SR141716A and naltrexone hydrochloride were obtained from the National Institute on Drug Abuse (Research Technical Branch, Rockville, MD, USA). The Δ^9-THC arrived in an alcohol solution and was isolated after arrival by lyophilization and stored frozen in aliquots. Both Δ^9-THC and SR141716A were each prepared as an emulsion using alcohol, emulphor and saline (1:1:18) prior to use. Naltrexone was dissolved in saline. The volume for both control (saline or vehicle) and drug injections was 0.1 ml/100 g b.wt. and the route of administration was always intraperitoneal. Naltrexone, Δ^9-THC and SR141716A were administered 20, 30 and 40 min, respectively, before the start of an experimental session. For comparison purposes, saline or vehicle was administered before the start of 15 or more experimental sessions at the times mentioned above. The subjects were generally tested 7 days a week. Dosages of Δ^9-THC were administered in a mixed order twice a week during the acute phase of the study; however, when the highest dose of Δ^9-THC (10 mg/kg) was administered the subjects were given drug only once a week.

2.5. Data analysis

Data from both components of the multiple schedule were analyzed in terms of the overall responses rate (response/min, excluding timeouts) and the overall accuracy or percentage of errors [(errors/total responses) $\times$ 100]. Each subject served as its own control. Control sessions during the

acute phase included occasions in which saline or vehicle was administered to subjects and at least five experimental sessions (no injections) that preceded the chronic phase of the study. The data from each subject were analyzed by comparing the range of variability for drug sessions with the range of variability for control sessions. A drug was considered to have had an effect to the extent that the mean data for a given dosage fell outside of the ranges of variability established for the control sessions. The percentage of errors was not included in the data analysis when response rate was less than 5 responses/min because of the small number of responses involved.

Within-session changes in responding were monitored by a cumulative recorder and a computer. In the acquisition component, learning was indicated by a within-session reduction in errors; i.e., a decrease in the number of errors between food presentations as the session progressed. Also, within-session error reduction was quantified by plotting the mean number of errors per 60 responses (1 bin = 60 responses). If the sequence was acquired, the cumulative-error curve asymptoted indicating within-session error reduction, otherwise the curve increased linearly. Cumulative-error curves may also demonstrate the disruption of learning even in cases where the overall percentage of errors falls within the range of variability established by control sessions (e.g., if a low, but constant, number of errors are made across a session and within-session error reduction does not occur).

3. Results

Stable responding was obtained in all subjects under both components of the multiple schedule after an average of 152 sessions. Measures of both rate and accuracy for each subject remained stable during control sessions (acute phase). Acquisition, which usually occurred a short time after the start of the session (5–10 mins), was characterized by a decrease in the number of incorrect responses and an increase in the number of consecutive correct completions of the response sequence.

In Fig. 1, the overall response rate and percentage of errors are shown for each subject during control sessions (saline or vehicle), and sessions in which SR141716A (0.32 and 1 mg/kg), naltrexone (0.32 and 1 mg/kg) or Δ^9-THC (1–10 mg/kg) was administered alone (acute phase). When varying doses of Δ^9-THC were administered acutely to the four subjects, dose-dependent decreases in overall response

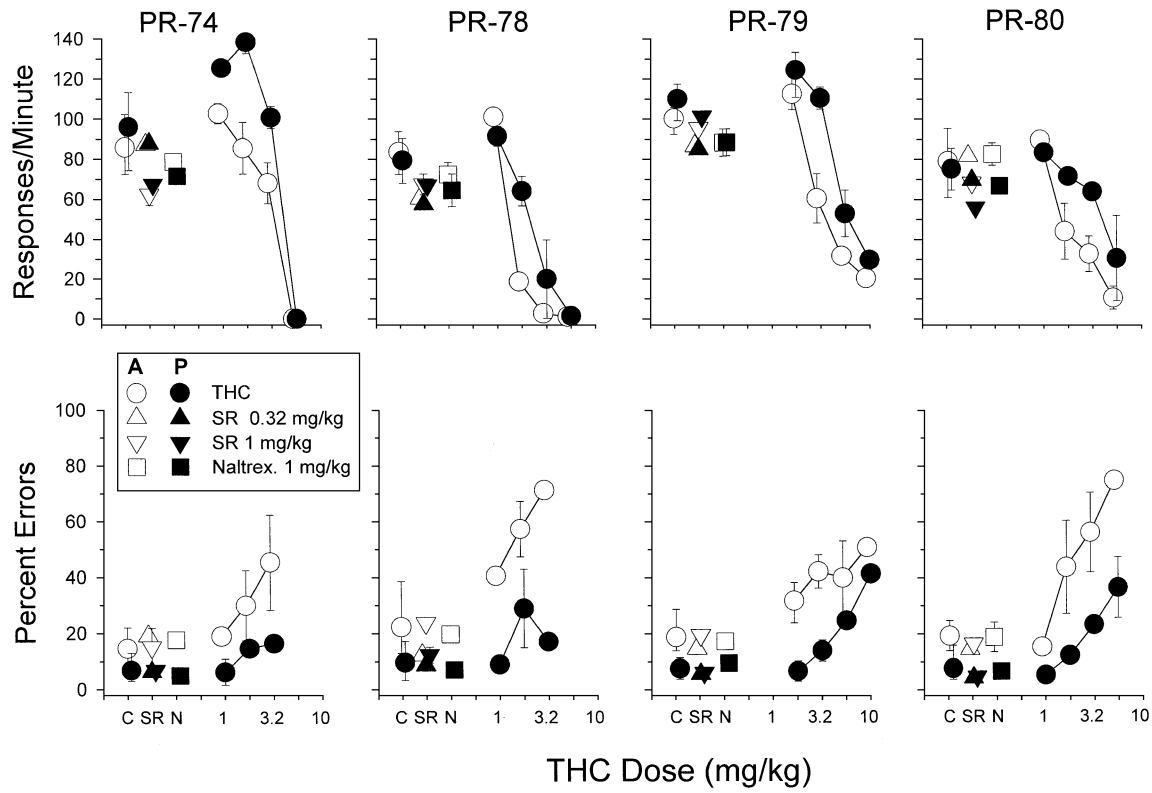

Fig. 1. The acute effects of Δ^9-THC on the overall response rate and percentage of errors in the acquisition and performance components of the multiple schedule in subjects PR-74, -78, -79 and -80 during the prechronic phase. Dose–effect data for the acquisition component are represented by the open symbols, whereas data from the performance component are represented by the filled symbols. Points and vertical lines above C indicate the mean and range for 7–19 vehicle or saline (control) sessions. The data points and vertical lines in the dose–effect curves indicate the mean and range for one to three determinations of that dosage; data points without vertical lines indicate either a single determination of that dose or an instance in which the range is encompassed by the data point.

rate occurred in the acquisition and performance components. However, at intermediate doses, the rate-decreasing effects were larger in the acquisition component than in the performance component. For example, in three of the four subjects, the magnitude of the decrease in the overall response rate at 1.8 mg/kg of Δ^9-THC was larger in the acquisition component than in the performance component when compared to the control data for each subject.

Δ^9-THC also produced dose-dependent increases in the overall percentage of errors in both components of the multiple schedule. However, when intermediate doses of Δ^9-THC were administered, accuracy in the acquisition component was disrupted more than in the performance component. For example, when 3.2 mg/kg of Δ^9-THC was administered to each subject, the magnitude of the increase in the overall percentage of errors was larger in the acquisition component than in the performance component when compared to the control data for each subject. As shown in Fig. 1, SR141716A and naltrexone produced little or no disruption in either response rate or the percentage of errors in the acquisition or performance components.

Fig. 2 depicts data from sessions in which 5.6 mg/kg of Δ^9-THC was administered daily for 22–30 days during the chronic phase. In all of the subjects, this dose initially produced large decreases in the overall rate of responding in both components and large increases in the overall

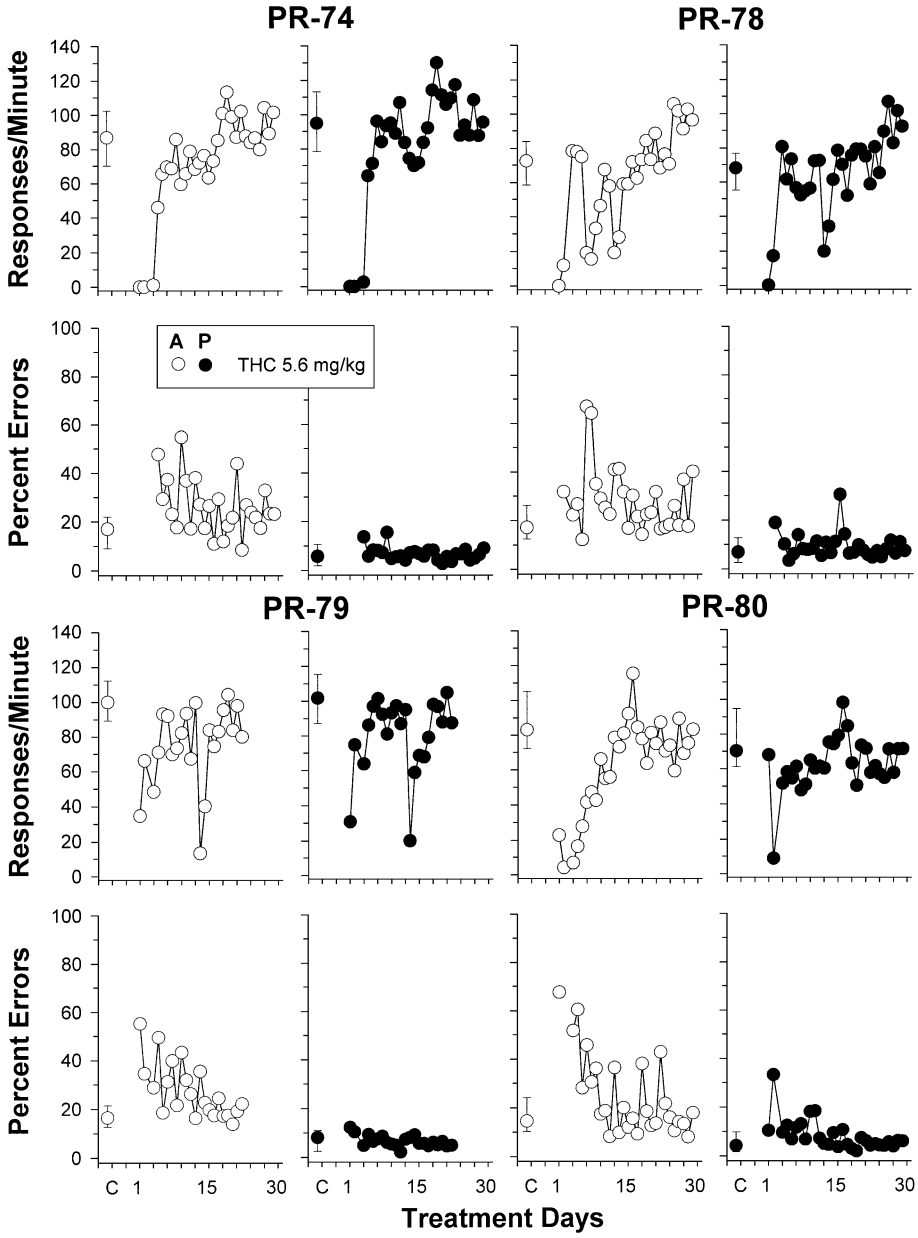

Fig. 2. The effects on overall response rate and percentage of errors when 5.6 mg/kg of Δ^9-THC was administered for 22–30 days before the start of the experimental session. Each subject's data are separated into four graphs (i.e., response rate and percent errors for both the acquisition and performance components). For additional details, see the caption for Fig. 1.

percentage of errors in the acquisition component when compared to control sessions. However, within 10 days, responding in both components was similar to the control range of responding, indicating the development of tolerance to the disruptive effects of Δ^9-THC. These data also show that while the disruptive effects on responding in both components were reduced over time, tolerance to the rate-decreasing effects in both components was probably more complete than tolerance to the error-increasing effects of Δ^9-THC in the acquisition component of the multiple schedule.

Data from sessions in which 1 mg/kg of SR141716A or naltrexone was substituted for the chronic dose of Δ^9-THC are presented in Fig. 3. The first two single bars in this graph represent the response rate and percent errors obtained during control sessions (C) and during the final 5 days of the chronic phase with 5.6 mg/kg of Δ^9-THC (T). The paired bars (solid and hatched) represent the respective effects of SR141716A (SR) and naltrexone (N) during the acute phase (solid) and chronic phase (hatched). As shown, SR141716A during the chronic phase produced little or no change in the response rate or accuracy in subjects PR-74 and -78, but produced a marked increase in the overall percentage of errors in the acquisition component in subjects PR-79 and -80 when compared to the acute, prechronic

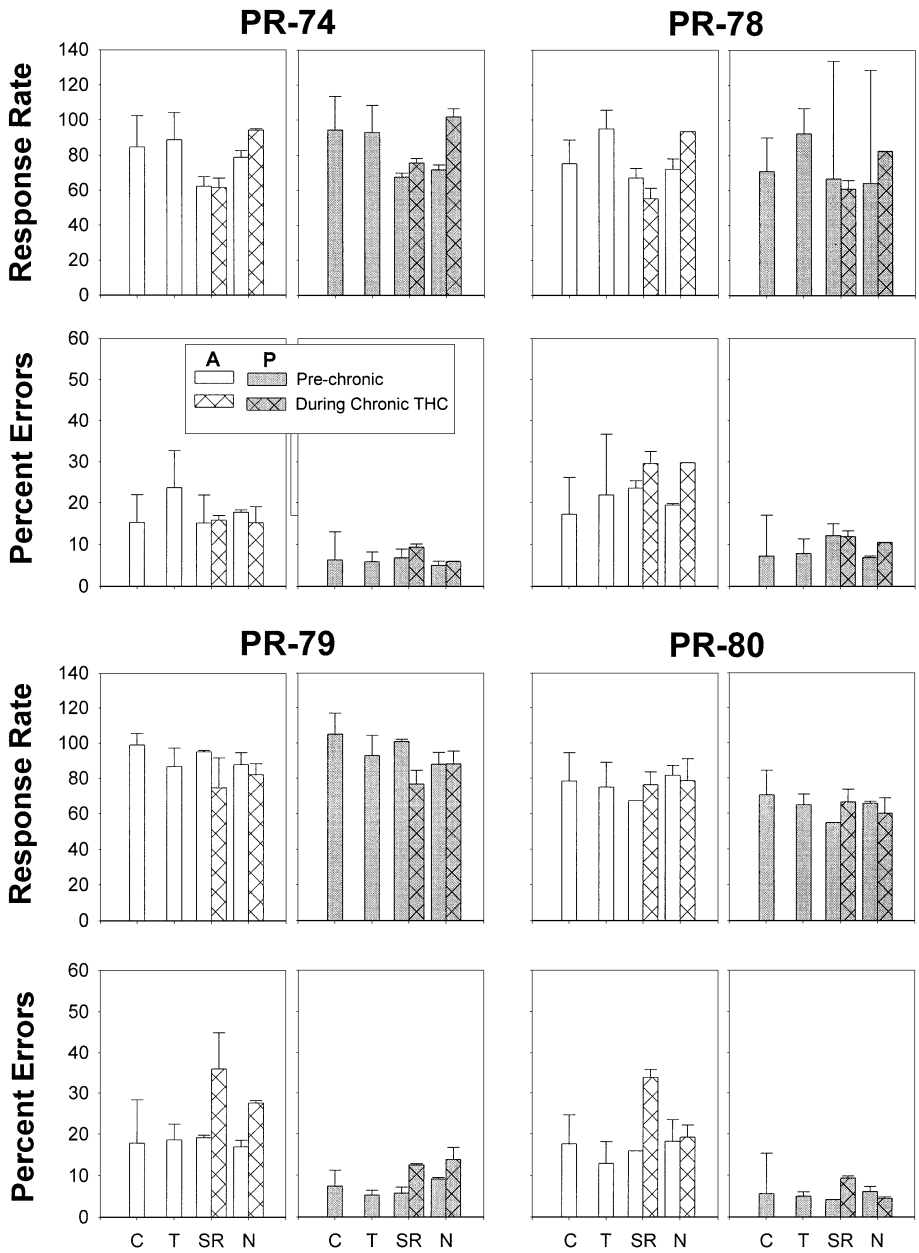

Fig. 3. The effects of both 1 mg/kg of SR141716A and 1 mg/kg of naltrexone, respectively, on overall response rate and percent errors during the acute and chronic phases of the study. Data for occasions in which SR141716A or naltrexone were administered during the chronic phase are represented by the hatched bars. Similar to Fig. 2, each subject's data are presented in four separate graphs. For additional details, see the caption for Fig. 1.

administration of the same dose. In contrast to SR141716A administration, only one subject (PR-79) showed any apparent disruptions in acquisition errors or rate of responding when naltrexone was substituted for Δ^9-THC.

The within-session pattern of errors during sessions when either 1 mg/kg of SR141716A or naltrexone was substituted for the chronic dose of Δ^9-THC is shown in Fig. 4. While little or no change occurred in responding when saline was substituted for chronic Δ^9-THC (for 15 consecutive days in all subjects) or when daily Δ^9-THC was intentionally suspended (no injection) for 1 day in subjects PR-74, -78 and -79 (data not shown), the pattern of errors was disrupted when 1 mg/kg of SR141716A was substituted for the chronic dose of Δ^9-THC. These disruptions in learning were demonstrated by the linear increase in the cumulative-error curves, i.e., the mean number of cumulative errors made per 60 responses was outside the range of variability established by the control sessions for three of the four subjects (PR-78, -79 and -80). Unlike Fig. 3, the cumulative-error curves for each subject in Fig. 4 show disruptions in accuracy that were not revealed by the overall measures of accuracy (based on session totals). Similar to the overall measures shown in Fig. 3, there were little or no disruptions in the within-session pattern of errors when naltrexone was substituted for chronic Δ^9-THC, except in subject PR-78. This difference highlights the importance of examining the pattern of errors across a session as another dependent measure of responding.

Cumulative records depicting the within-session patterns of responding for subject PR-80 are shown in Fig. 5. The record in the first row shows the response pattern for this subject when 1 mg/kg of SR141716A was administered

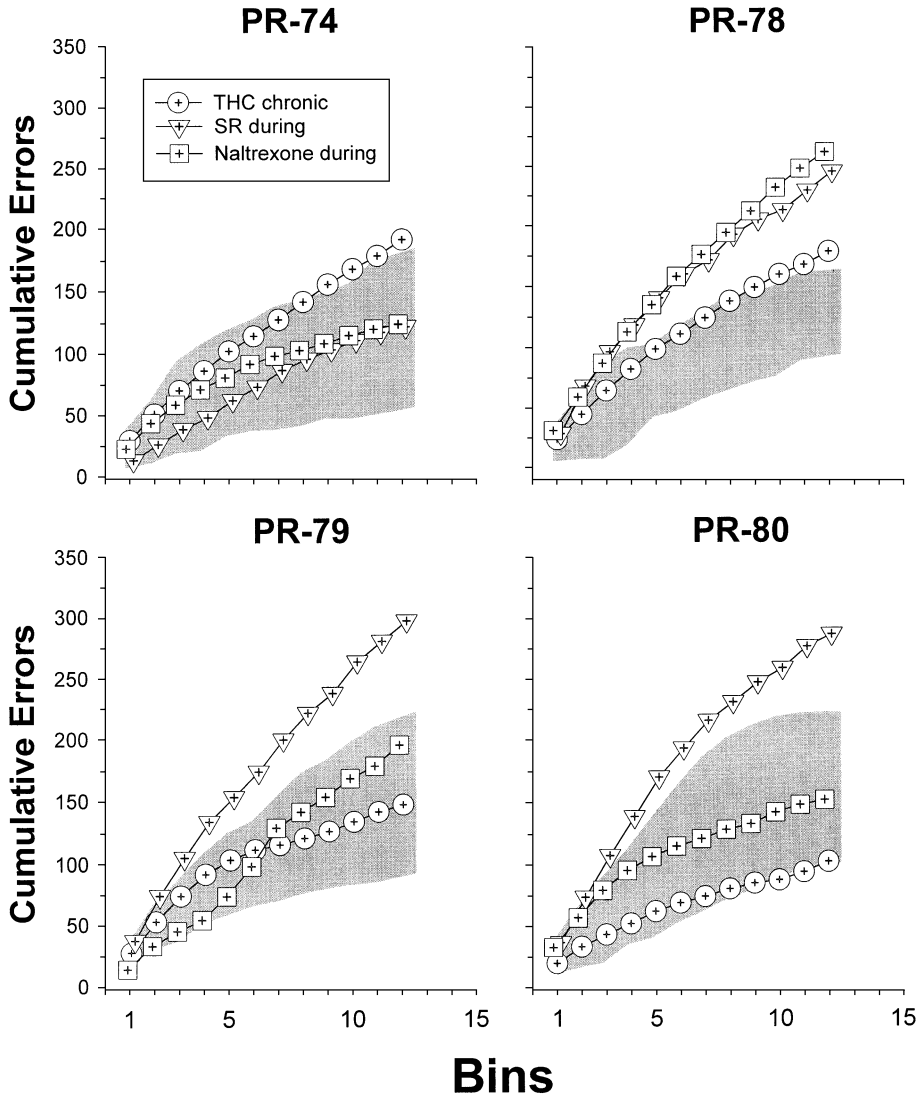

Fig. 4. Effect of substituting 1 mg/kg of either SR141716A or naltrexone for the chronic dose of Δ^9-THC on within-session error reduction. The cumulative number of errors for these sessions is plotted in response bins, with each bin representing the mean number of errors emitted every 60 responses. The area shaded in gray represents the control range for each subject, which was established with injections of vehicle or saline prior to chronic treatment with 5.6 mg/kg of Δ^9-THC.

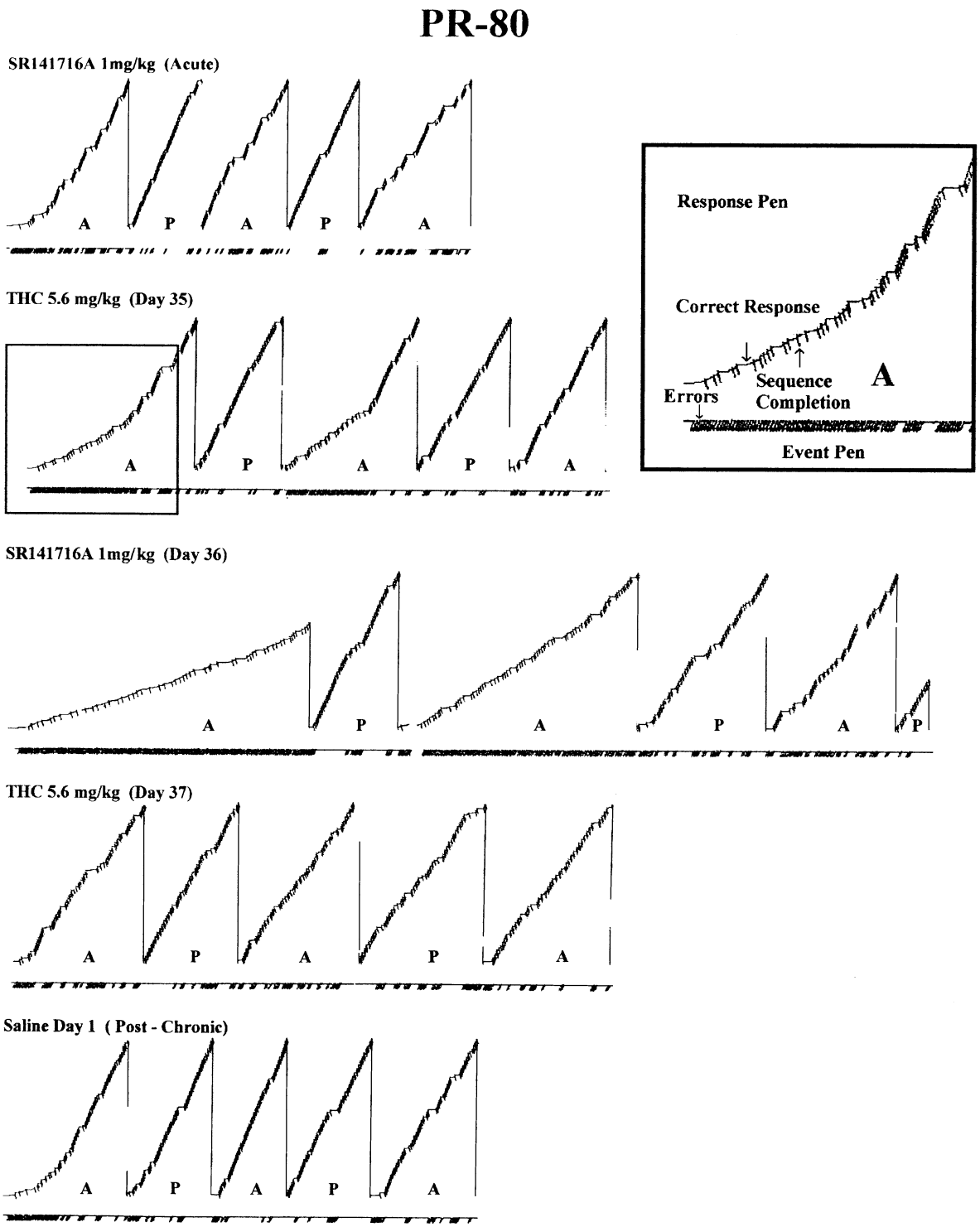

Fig. 5. Cumulative records depicting the within-session patterns of responding obtained when chronic Δ^9-THC (Days 35 and 36), 1 mg/kg of SR141716A (prechronic or substituted for Δ^9-THC) or saline (postchronic) was administered to subject PR-80. The response pen stepped upward with each correct response and was deflected downward after the three-response sequence was completed. Errors are indicated by deflections of the event pen (below each record). The response pen reset at the completion of each component. Each session began with an acquisition component, which alternated with a performance component after 40 reinforcers or 20 min, whichever occurred first. Each session terminated after 200 reinforcers or 100 min, whichever occurred first.

during the acute phase. This record shows the characteristic pattern of within-session error reduction that occurred in the acquisition component, and the comparatively errorless responding that occurred in the performance component. Note that fewer errors and more consecutive correct responding occurred in the second acquisition component

when compared to the first acquisition component indicating that acquisition had occurred.

A similar pattern of within-session responding was evident when 5.6 mg/kg of Δ^9-THC was administered chronically (rows 2 and 4), and when saline was administered during the post-chronic phase (row 5). However, when 1 mg/kg of SR141716A was substituted for the daily dose of Δ^9-THC (row 3), the pattern of responding in the acquisition component was disrupted. SR141716A produced a selective decrease in accuracy of responding that was evident during the first two acquisition components. In addition, the pattern of responding was substantially different than the pattern seen when the same dose of SR141716A was administered during the acute phase (row 1) and different from the pattern seen when saline was administered following termination of chronic Δ^9-THC (row 5).

Fig. 6 shows the redetermination of the acute effects of Δ^9-THC 7–12 weeks after the chronic administration of Δ^9-THC was terminated. As shown in this figure, subjects PR-78 and -80 were less sensitive to the rate-decreasing effects of Δ^9-THC in both components of the multiple schedule, whereas all of the subjects were generally less sensitive to the error-increasing effects of Δ^9-THC in both components. Note that the dose–effect curves determined for Δ^9-THC

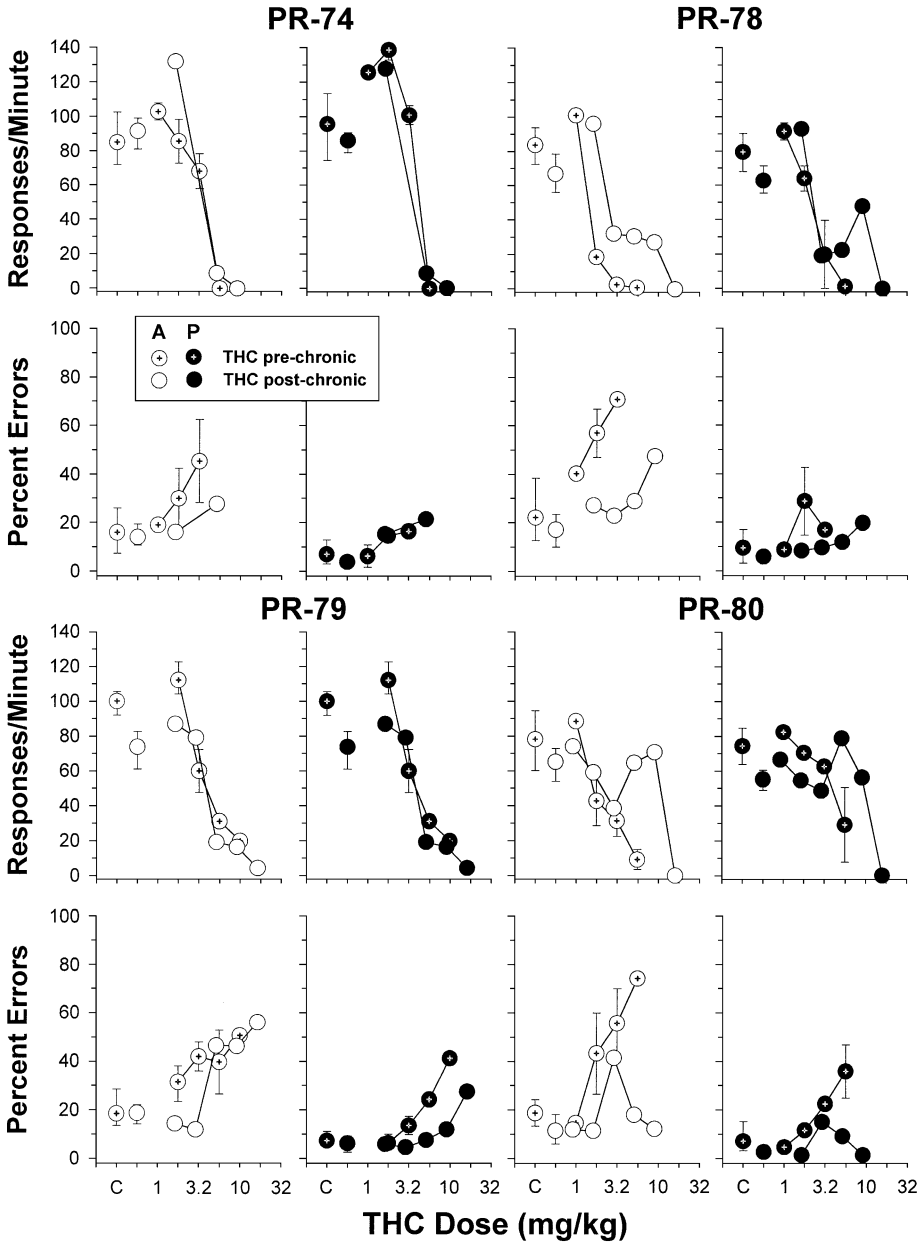

Fig. 6. The effects of Δ^9-THC on the overall rate of responding and percentage of errors, 7–12 weeks after the termination of chronic Δ^9-THC. The dose–effect curve for Δ^9-THC, determined before the chronic phase, is indicated by the plus sign in the symbols. Data points for the control sessions (postchronic) represent the mean and range for five to seven sessions. For additional details, see the caption for Fig. 1.

postchronically were shifted 1/4 to 1/2 log-unit to the right of the dose–effect curves determined during the acute phase.

4. Discussion

When administered acutely to all of the subjects, varying doses of Δ^9-THC consistently produced decreases in the overall response rate and increases in the overall percentage of errors in both the repeated-acquisition and performance components. Δ^9-THC also produced greater disruptions in the acquisition component than in the performance component. These data are consistent with and replicate previous reports demonstrating that Δ^9-THC can produce disruptions in complex operant behavior in humans, nonhuman primates and rats (Branch et al., 1980; Brodkin and Moerschbaecher, 1997; Nakamura-Palacios et al., 2000; Winsauer et al., 1999a).

During sessions when 0.32 or 1 mg/kg of either SR141716A or naltrexone was administered acutely to rats responding under the multiple schedule, little or no disruption occurred in the overall response rate or accuracy in either component at the doses tested. Although these doses have previously been shown to antagonize the effects of cannabinoid agonists such as Δ^9-THC and mu-opioid receptor agonists such as morphine (Brodkin and Moerschbaecher, 1997; Walker et al., 1994), respectively, these data with SR141716A and naltrexone are consistent with data from several studies demonstrating that much higher doses of both SR141716A and naltrexone alone are needed to disrupt operant responding in rats (Adams and Holtzman, 1990; Brodkin and Moerschbaecher, 1997; Oliveto et al., 1991). For example, Brodkin and Moerschbaecher (1997) demonstrated that SR141716A only produced disruptions in the overall response rate and accuracy when 32 mg/kg of SR141716A was administered to rats responding under a similar repeated-acquisition task. Also, previous reports have indicated that cumulative doses of 30 mg/kg or higher of naltrexone were necessary to produce rate-decreasing effects under several different operant schedules of reinforcement (Adams and Holtzman, 1990; Oliveto et al., 1991).

Tolerance to the effects of Δ^9-THC has been studied rather extensively in humans, nonhuman primates, dogs and rodents (Branch et al., 1980; Fan et al., 1994; Ferraro and Grisham, 1972; Jones et al., 1976, 1981; Lamb et al., 2000; Manning, 1973; McMillan et al., 1983), and using a variety of measures including operant behavior (Branch et al., 1980; Lamb et al., 2000; McMillan et al., 1983). Previous reports have demonstrated that the development of tolerance can be modulated by behavioral variables such as reinforcement density and stimulus control (Schuster et al., 1966; Thompson, 1974; Thompson and Moerschbaecher, 1978, 1979). For example, Schuster et al. (1966) demonstrated that the loss of reinforcement modulated the development of tolerance to amphetamine in rats responding under a multiple fixed-interval (FI), differential reinforcement of low rates (DRL) schedule. Although tolerance tended to be more complete for responding in the performance component, data from the present study are inconsistent with findings from Thompson (Thompson, 1974), which demonstrated that tolerance developed faster in the performance component because of the presence of strong stimulus control (Thompson, 1974; Thompson and Moerschbaecher, 1978, 1979). Given the difference in the behaviors examined in the two studies, further work will be needed to address the importance of these two variables in the chronic effects of cannabinoids.

In previous studies that used operant procedures with nonhuman primates (Beardsley et al., 1986) and rats (Beardsley and Martin, 2000), dependence on Δ^9-THC was indicated by a disruption of response rate when chronic drug treatment was terminated (e.g., spontaneous withdrawal) or when the CB1 receptor antagonist SR141716A was administered during chronic drug treatment (e.g., precipitated withdrawal). For example, Beardsley and Martin (2000) demonstrated the disruption of response rate when 1 mg/kg of SR141716A was administered to rats that were treated chronically with 40 mg/kg of Δ^9-THC. In the present study, the same dose of SR141716A disrupted both response rate and accuracy in the acquisition component when it was substituted for a much smaller chronic dose of Δ^9-THC (5.6 mg/kg), suggesting that substantially lower doses of Δ^9-THC may produce dependence in rats following repeated administration.

Seven to twelve weeks after the termination of the chronic administration of Δ^9-THC, the acute effects of Δ^9-THC were redetermined and all of the subjects demonstrated tolerance to its disruptive effects. This demonstrated the persistence of tolerance over time. Previous reports have indicated that CB1 receptors are downregulated in various brain areas such as the cerebellum and striatum for more than 8 weeks following the termination of the chronic administration of Δ^9-THC in rodents (Rodriguez et al., 1994; Sim et al., 1996; Westlake et al., 1991; Zhuang et al., 1998). McMillan et al. (1971) have also reported the maintenance of tolerance to the effects of Δ^9-THC on schedule-controlled responding in pigeons and to the physiological effects seen in dogs several weeks after the termination of the chronic administration of Δ^9-THC.

Previously, behavioral studies on the effects of chronic administration of Δ^9-THC have examined its effects on the quantity of behavior (e.g., rate of responding or locomotor activity). In those studies, changes in the quantity of behavior during chronic treatment were characterized by measures such as catalepsy and ataxia or by decreases in response rate. To extend these findings, the present study examined the effects of chronic Δ^9-THC on learning and included measures of both the quantity and quality of behavior under two different behavioral tasks. Data from the present study demonstrated how the quality of behavior

may be a more sensitive measure than the quantity of behavior as evidenced by the selective disruptions in within-session error reduction, without changes in response rate. For example, when SR141716A was substituted for the chronic dose of Δ^9-THC, accuracy in the acquisition component was selectively disrupted. This selective disruption of responding was consistent with previous reports (Thompson, 1974; Thompson and Moerschbaecher, 1979), which demonstrated that behavior under relatively weak stimulus control is more sensitive to drug effects than behavior under relatively strong stimulus control. To what extent the loss of reinforcers or stimulus control may have contributed to these findings remains to be investigated. In summary, tolerance developed across the behavioral tasks and responding in each task was differentially sensitive to the disruptive effects of SR141716A during chronic treatment with Δ^9-THC.

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