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Schedule-dependent Tolerance to Behavioral Effects of Δ^9-Tetrahydrocannabinol when Reinforcement Frequencies are Matched[1]

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GALBICKA, G., D. M. LEE AND M. N. BRANCH. *Schedule-dependent tolerance to behavioral effects of Δ^9-tetrahydrocannabinol when reinforcement frequencies are matched.* PHARMAC. BIOCHEM. BEHAV. 12(1) 85–91, 1980.—Squirrel monkeys pressed a lever under a multiple interresponse-time >28-sec, modified random-interval schedule which provided comparable frequencies and temporal distributions of food pellet presentation in the two components. Daily intramuscular administration of either 0.25 or 1.00 mg/kg Δ^9-tetrahydrocannabinol resulted initially in suppression and/or disruption of responding and concomitant decreases in the frequency of food presentation in both components. Responding in both components next increased, resulting in recovery of baseline frequencies of pellet delivery during the random-interval component, but continued depression during the interresponse-time schedule. The drug-induced changes in responding under the interresponse-time schedule diminished with repeated injections, whereas response rates during the random-interval schedule sometimes remained elevated. Interresponse-time distributions under the interresponse-time schedule showed that with repeated administration of the drug only those characteristics which had the greatest effect on reinforcement frequency recovered to baseline levels. When drug injections were replaced by daily injections of the vehicle, responding was greatly disrupted only during the random-interval component. These findings are only partially consistent with other results which suggest that tolerance development to the behavioral effects of Δ^9-tetrahydrocannabinol is greatly enhanced if the drug initially produces reinforcement loss.

Tolerance Δ^9-Tetrahydrocannabinol Schedule-controlled behavior Interresponse-times Squirrel monkeys

REPEATED administration of Δ^9-tetrahydrocannabinol (Δ^9-THC) to subjects responding under various schedules of food presentation often leads to a decrease in its effects, indicating the development of tolerance [8, 9, 14, 15, 16, 17]. Ferraro [5, 6, 7] has compiled data which suggest a role for reinforcement loss in the development of tolerance to the behavioral effects of Δ^9-THC. Specifically, he has shown that tolerance has been more likely to develop (or quicker to develop) if administration of the drug initially produced adverse effects on the behavior-environment relationship, such as a decrease in reinforcement frequency or an increase in the frequency of aversive events. This is an extension of a "cost hypothesis" of tolerance development, formulated by Schuster, Dockens and Woods [18], which states that tolerance will develop to the initial effects of a drug if "the action of the drug is such that it disrupts the organism's behavior in meeting the environmental requirements for reinforcement," (p. 181). More recently this hypothesis has been called "the reinforcement density hypothesis" [2].

Most data offered in support of a "cost" account of tolerance development to Δ^9-THC's effects involve between-subject comparisons. Typically, some subjects show reinforcement loss following initial administration of Δ^9-THC while others do not, with the former being more likely to develop tolerance if the drug is administered repeatedly [5,15]. A few studies have reported comparisons of tolerance development in single subjects responding under two successively alternating schedules [4, 11] wherein tolerance to behavioral effects of Δ^9-THC generally developed at different rates depending on the schedule that controlled responding. Tolerance development was generally correlated with an initial drug-induced decrease in reinforcement frequency.

In no study, however, has reinforcement frequency been equated before making comparisons. Elsmore [4] nominally equated reinforcement frequency when he compared development of tolerance to behavioral effects of Δ^9-THC in rhesus monkeys responding under either a fixed-interval 120-sec schedule in which the first response after an interval of 120 sec produced food, or an IRT>120-sec schedule in which food was presented for any response that followed the immediately preceding response by more than 120 sec.

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Elsmore programmed the schedules in alternating 5-min components and equated the overall number of reinforcements delivered per session by allowing only one food presentation during each component. When the subject produced food, the stimulus lights were turned off and a blackout remained in effect for the duration of the component. While this procedure did equate the number of reinforcements delivered in the presence of each stimulus, it did not equate the time between reinforcements and therefore reinforcement frequency. Since the rate of reinforcement plays a powerful role in the control of conditioned behavior [1, 3, 12] it would seem important to equate baseline reinforcement frequency when examining the development of tolerance as a function of the presence or absence of drug-induced changes in that variable. Additional support for this position comes from a recent review of the literature on behavioral tolerance [2] in which the authors noted that "It is clearly advisable to attempt to equate baseline reinforcement densities when attempting to assess the role of this factor in tolerance development" (p. 438). Thus, while reinforcement loss may indeed to be a major determinant of the rapidity and degree of tolerance development as Ferraro [5, 6, 7] has suggested, statements to that effect seem premature in the absence of the proper control for differences in reinforcement frequency under baseline conditions.

The purpose of the present study, therefore, was to examine the role of reinforcement loss in the development of tolerance to Δ^9-THC under conditions where contingencies controlling behavior provided similar frequencies and temporal distributions of reinforcement under baseline conditions but which differed with respect to the effects of response-rate changes on reinforcement rate. Specifically, squirrel monkeys were trained to respond under a multiple schedule in which the frequency and temporal distribution of food presentation in the two components were comparable under baseline conditions. Rate of food presentation was highly dependent on response patterning and rate in one component of the schedule, while in the other component variations in response rate had comparatively little effect on the frequency of food presentation. Development of tolerance to the disruptive effects of Δ^9-THC under this arrangement was examined with respect to the presence or absence of drug-induced disruptions in the frequency of reinforcement.

METHOD

Subjects

Four adult male squirrel monkeys (*Saimiri sciureus*) were used. Monkeys 501, 504, and 519 were experimentally and drug naive at the beginning of the experiment. Monkey 509 had been exposed previously to a multiple variable-ratio, variable-interval schedule of food presentation and had been administered several doses of Δ^9-THC, the last dose 345 days prior to the beginning of this experiment. The monkeys were individually housed and maintained at 85% of their free-feeding weights; 720, 850, 765, and 900 g for monkeys 501, 504, 509, and 519, respectively. Vitamin-enriched water was continuously available in the home cages.

Apparatus

Experimental sessions were conducted in a clear Plexiglas restraint unit similar to one previously described [10]. The monkeys were restrained at the waist in a sitting position by a Plexiglas waist plate 16 cm above, and parallel to a grid floor. This allowed free movement of the head, limbs, and torso. The waist plate positioned the monkey 10 cm from the front wall of the unit which contained a response lever (Coulbourn Instruments, Model E21-03) and a recessed food cup. Lever presses with a downward force in excess of 0.4 N closed a microswitch, briefly operated a feedback relay, and were recorded as responses. P. J. Noyes precision food pellets (190 mg, banana-flavored) could be delivered into the food cup through operation of a Gerbrands (Model D-1) pellet dispenser. Three pairs of 1.1-W, 28 VDC colored stimulus lamps were arranged horizontally behind the front wall 18 cm above the waist plate. The power source for these lights was independent of power used for other control functions. During experimental sessions the restraint unit was placed in a ventilated, sound-attenuating enclosure in a room with white noise continuously present. A PDP-8F minicomputer operating under the SKED software system [19] arranged environmental events and collected data. Cumulative response records of each session were generated by a Ralph Gerbrands, Co. (Model C-3) cumulative recorder.

Procedure

The subjects, except 509, were initially placed in the chamber under conditions in which each response produced a food pellet. After two sessions (50 pellets each) of training, lever presses with interresponse times greater than 5 sec (IRT>5-sec) produced food. That is, pellets were delivered only for a response which followed the immediately preceding response by 5 sec or more. The IRT requirement was gradually increased in 4- or 5-sec steps up to 28 sec. After responding had stabilized under the IRT>28-sec procedure, a multiple IRT>28-sec, random-interval (RI) schedule was introduced. Because lever pressing had previously been established as part of Monkey 509's repertoire, extensive pretraining was not required and this monkey was exposed directly to the multiple IRT>28-sec, RI schedule. Under this procedure, responses in the presence of a pair of blue stimulus lamps produced pellets according to the IRT>28-sec schedule. Responses in the presence of a pair of white stimulus lamps produced pellets according to the RI schedule. Under the RI schedule, pellet availability was determined by a probability generator that was sampled once per second, beginning 28 sec after the previous pellet delivery. The first response after a pellet was made available produced the pellet. The probability of pellet availability was adjusted for each animal to equate the frequencies of delivery under the two schedules. This resulted in similar interpellet distributions and a minimum interpellet interval of 28 sec under both schedules. The resulting RI values were approximately 28, 50, 40, and 56 sec for Monkeys 501, 504, 509, and 519, respectively. Components alternated every 5 min. Sessions began with the IRT >28-sec component, terminated after the fourth RI component, and were conducted daily.

Δ^9-tetrahydrocannabinol was obtained from NIMH [(−)-trans-Δ^9-THC, 95% in dehydrated alcohol, 25 mg/5.3 ml]. The alcohol was evaporated and the residue suspended in a 10% (V/V) solution of Polysorbate 80 (Tween 80) in 0.9% NaCl solution. The drug was stored in refrigerated (4°C) darkness. Intramuscular injections were made 60 min prior to a session, the volume of the injections being 0.25 ml/kg of body weight. The subjects remained in their home cages between the time of injection and the beginning of a session.

After stable performance was engendered under non-drug

conditions, Monkey 501 received twenty consecutive daily injections of 0.25 mg/kg Δ^9-THC, followed by ten consecutive daily injections of vehicle. Monkey 504 began a series of daily administrations of 0.25 mg/kg that had to be terminated after 21 days because of a leg infection. After 117 days the series was restarted. All monkeys were later exposed to a series of daily injections of 1.00 mg/kg Δ^9-THC followed by a series of daily injections of the vehicle. For Monkeys 501 and 504, a series of 20 daily injections of 1.00 mg/kg Δ^9-THC, which began 274 and 176 days, respectively, after the termination of the previous chronic series, was followed by a series of 10 daily vehicle injections. Since stable effects of Δ^9-THC were not obtained by the end of twenty days with the other two subjects, injections of 1.00 mg/kg Δ^9-THC (and subsequent vehicle injections) for Monkeys 509 and 519 were not terminated after a fixed number of sessions, but continued until response rates, reinforcement rates, and IRT distributions concurrently showed no systematic changes for 10 consecutive daily sessions. These criteria resulted in both animals receiving 30 consecutive daily injections of Δ^9-THC, followed by vehicle injections for 24 and 45 days for Monkeys 509 and 519, respectively.

RESULTS

Panels A and C of Fig. 1 show representative cumulative records of responding under control conditions for Monkeys 501 and 504. The multiple schedule produced two distinct rates and patterns of responding. All monkeys responded at a low, constant rate of approximately two responses per minute during the IRT>28-sec component. Response rates under the RI schedule varied widely among subjects, from approximately five responses per minute for Monkey 519 to approximately 45 responses per minute for Monkey 504. All monkeys, however, showed similar patterns of responding under this schedule. Pauses typically followed each pellet delivery under the RI schedule. After these initial pauses, responding occurred at a fairly high, constant rate until the next pellet was delivered. The multiple schedule maintained behavior appropriate to the individual components throughout the session, i.e., responding alternated between the low, constant rate associated with the IRT>28-sec component and the pause-respond pattern associated with the RI component.

The two line drawings in the lower portion of Fig. 1 show the interpellet distributions for the two control sessions. The distributions are similar and are typical of control sessions. Table 1 presents the means and ranges over the last 5 control sessions of three reinforcement measures; the number of pellets delivered, the mean interpellet interval, and the standard deviation of the interpellet distributions. Inspection of the values shows that in all cases mean numbers of pellets received in the two components were similar. Additionally, standard deviations of the distributions of interpellet intervals also were generally similar, although data for Monkeys 501 (before chronic administration of 0.25 mg/kg Δ^9-THC) and 509 reveal slightly larger standard deviations for the distributions from the IRT schedule. Figures 2 and 3 show response rates and number of pellets delivered in each component during the first and last five sessions under the different experimental phases. Baseline data are representative of the range of response and reinforcement rates for the previous 10 sessions. Drug effects were considered reliable only when obtained values fell outside this range.

The initial effect of administering either 0.25 mg/kg or 1.00 mg/kg Δ^9-THC (points under D in Figures 2 and 3, respectively) in all monkeys except 504 was to produce almost complete suppression of lever pressing, which resulted in

TABLE 1

MEANS AND STANDARD DEVIATIONS OF INTERPELLET-TIME DISTRIBUTIONS AND NUMBER OF PELLETS DELIVERED DURING BASELINE

		Mean (sec)	SD (sec)	N
501*	IRT	46.47 (40.83–53.26)	23.00 (17.61–26.58)	26.6 (23–30)
	RI	41.97 (39.71–45.05)	10.45 (8.64–11.59)	28.8 (27–30)
501†	IRT	42.86 (39.14–47.40)	17.58 (11.76–20.02)	28.8 (26–32)
	RI	44.50 (39.71–45.05)	13.10 (10.32–15.79)	27.4 (26–29)
504*	IRT	63.21 (56.13–67.80)	27.95 (27.81–44.69)	19.2 (17–21)
	RI	56.87 (43.39–74.22)	27.34 (15.41–52.12)	22.2 (16–28)
504†	IRT	49.72 (42.54–62.00)	26.85 (19.39–42.86)	24.8 (20–28)
	RI	50.72 (46.85–56.08)	18.77 (12.94–24.30)	23.2 (22–25)
509†	IRT	51.94 (45.37–65.66)	30.00 (20.92–37.02)	25.6 (19–32)
	RI	45.89 (42.41–50.40)	13.54 (11.12–15.34)	26.6 (23–29)
519†‡	IRT	69.40 (53.63–85.98)	45.03 (27.23–76.96)	17.6 (14–21)
	RI	74.44 (51.54–91.92)	40.63 (26.86–58.21)	15.4 (13–18)

*Prior to 0.25 mg/kg Δ^9-THC.

†Prior to 1.00 mg/kg Δ^9-THC.

‡Due to a data collection error, data for the five days immediately preceding chronic injection are not available. Data presented are from the 6th–10th days preceding chronic injection.

Values are means of the last five days; numbers in parentheses are ranges.

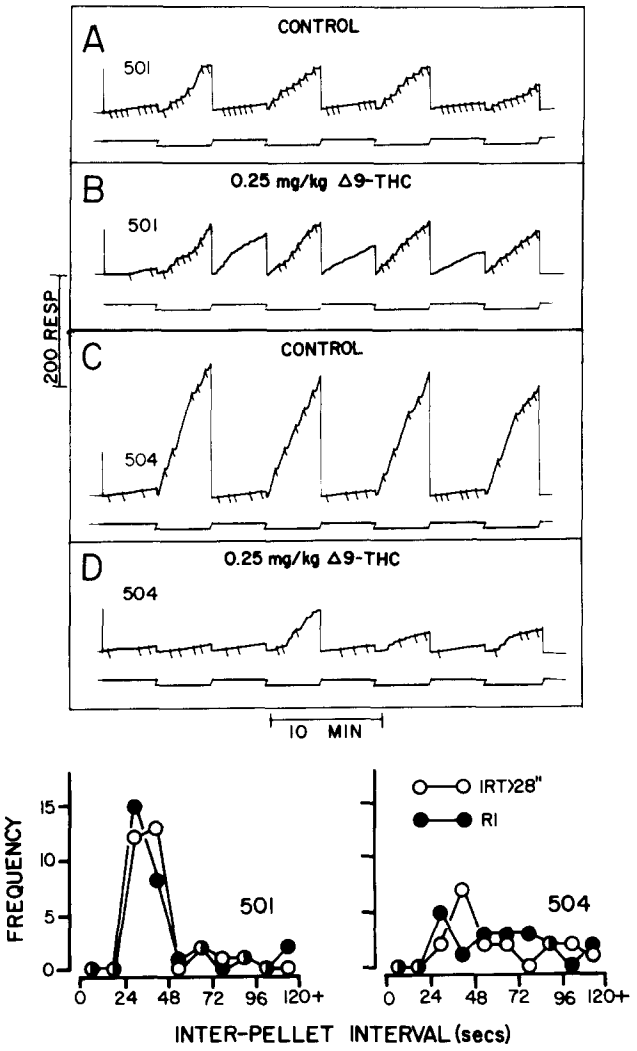

FIG. 1. Cumulative response records depicting performance for two subjects (501 and 504) under control conditions (panels A and C) and on the first day responding occurred following administration of 0.25 mg/kg Δ^9-THC (panels B and D). *Ordinate:* cumulative responses; *Abscissa:* time. The upper (response) pen stepped vertically with each response, deflected with each pellet delivery, and reset to baseline at the end of each component. The lower (event) pen remained up during IRT>28-sec components and deflected during RI components. The bottom two figures are interpellet-time distributions taken from the two control sessions presented above.

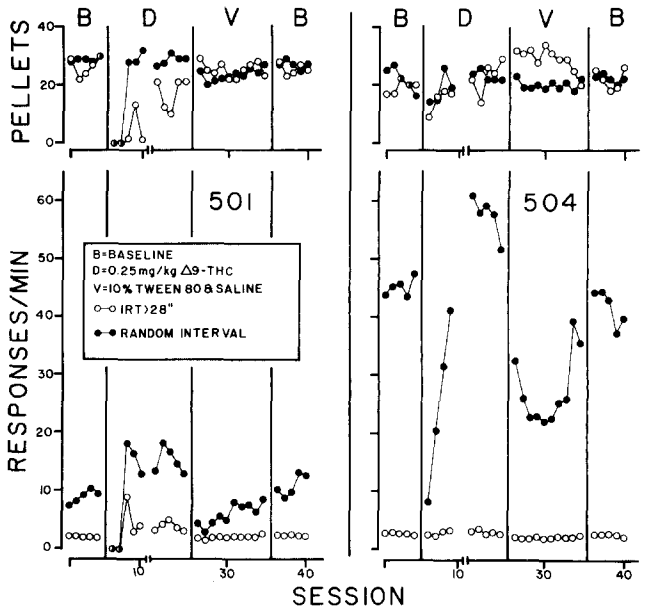

FIG. 2. Responses per minute and number of pellets delivered per session during the IRT>28-sec schedule (open symbols) and the RI schedule (closed symbols). *Ordinate:* response rate (lower graphs) or number of pellets delivered (upper graphs); *Abscissa:* consecutive experimental sessions. Data were taken from the last five days of baseline (first B), the first and last five days of chronic 0.25 mg/kg Δ^9-THC administration (D), days in which the vehicle was substituted for drug injections (V), and the first five days of baseline following daily injections of vehicle (second B). Data from session 10 for Monkey 504 are not presented due to apparatus failure.

decreases in the number of pellets delivered in both components for these monkeys. Monkey 504's mean response rate during the IRT component was little affected following the initial administration of either 0.25 or 1.00 mg/kg of Δ^9-THC, although responding during the RI component was greatly suppressed. While the average rate for this monkey during the IRT component did not change following the initial administration of Δ^9-THC, the temporal patterning of responding was disrupted (see Fig. 1, Panel D). This disruption, combined with the suppression of responding during the RI component following drug administration produced decreases in the frequency of food presentation during both components similar to, but of lesser degree than those observed with the other subjects.

With repeated administration of Δ^9-THC, response rates for Monkeys 501 and 509 increased to levels above baseline during the IRT component of the multiple schedule. A cumulative record illustrating this effect is presented in Panel B of Fig. 1. This record was taken from the first day Monkey 501 resumed responding following initiation of the chronic series (session 8 in Fig. 2). Increases in response rate resulted in continued decreases in the frequency of pellet delivery during this component (open points under D, upper panels in Figs. 2 and 3). These increases in response rate diminished somewhat with repeated administration of either 0.25 or 1.00 mg/kg Δ^9-THC, although complete recovery of baseline response rates was not observed. The frequency of pellet presentation during this component concomitantly increased with repeated Δ^9-THC administration to a point where the number of pellets delivered per session during the IRT>28-sec component was either about equal to or slightly less than the number delivered under baseline conditions. Repeated administration of Δ^9-THC to Monkeys 504 and 519 did not generally produce increases in response rate during the IRT component; responding simply recovered from the initial suppressive and/or disruptive effects of Δ^9-THC such that pellet frequencies comparable to baseline were produced.

Response rates increased during the RI component at least to baseline levels and in most cases to levels above baseline during repeated administration of Δ^9-THC. These increases restored the frequency of pellet delivery to baseline levels and did not tend to diminish with repeated injections, except when Monkey 509 was given chronic treatment with 1.00 mg/kg Δ^9-THC. Response rates in the RI

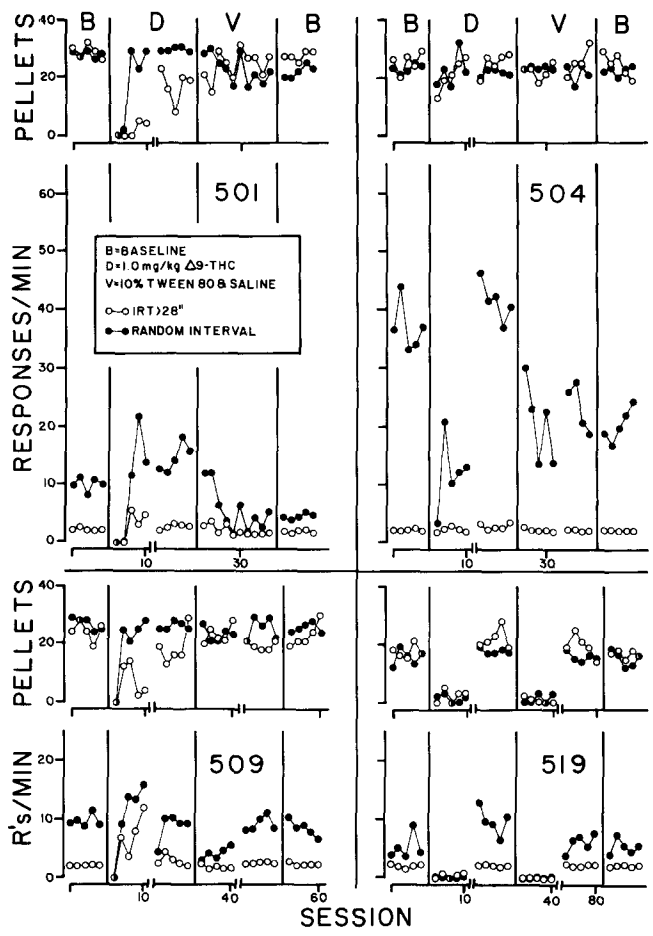

FIG. 3. Responses per minute and number of pellets delivered per session for Monkeys 501, 504, 509, and 519 during various experimental procedures. Points under D represent data taken from the first and last five days of chronic 1.00 mg/kg Δ⁹-THC administration. All other information is the same as for Fig. 2. Data from session 32 for Monkey 504 are not presented due to apparatus failure.

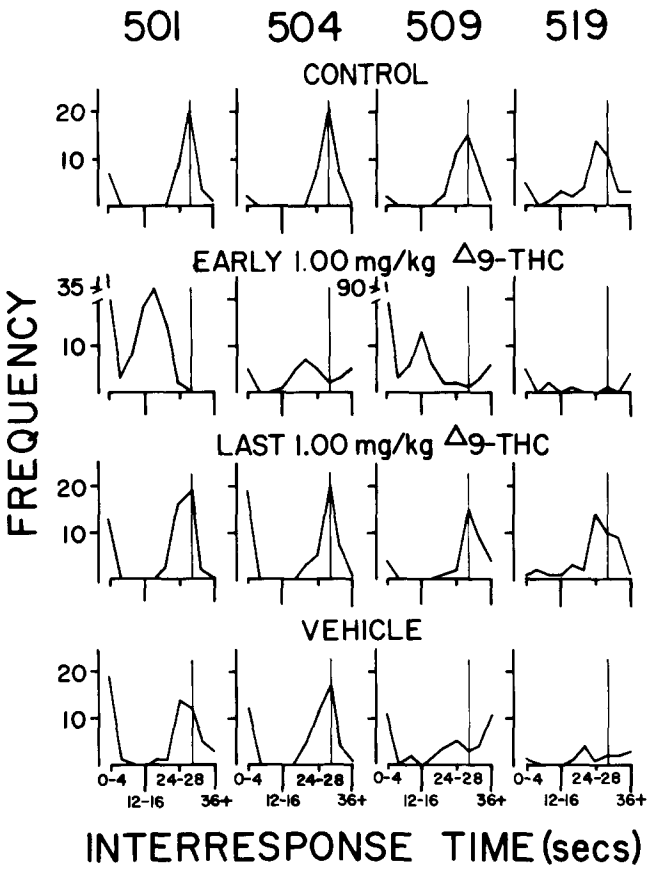

FIG. 4. Interresponse-time distributions for all subjects taken from the day immediately preceding initiation of chronic 1.00 mg/kg Δ⁹-THC administration (control), the first day in which responding occurred following Δ⁹-THC administration (early THC), the last day of Δ⁹-THC administration (last THC), and the day vehicle was first substituted for Δ⁹-THC (vehicle). IRTs to the right of the single vertical line produced food. *Ordinate:* Absolute frequency of interresponse-times; *Abscissa:* interresponse-time in 4-sec bins.

component for this monkey showed a gradual transition from the initial increases to rates approximating those attained under baseline.

Figure 4 shows in more detail the effects of Δ⁹-THC injections on responding during the IRT>28-sec component. Displayed are IRT frequency distributions for all subjects taken from the day immediately preceding the beginning of chronic 1.00 mg/kg Δ⁹-THC administration (control), the first day in which responding occurred during repeated Δ⁹-THC administration (early THC), the last day of Δ⁹-THC administration (last THC), and the day the vehicle was first substituted (vehicle). Under control conditions most IRTs were between 24 and 40 sec. The drug initially produced a substantial disruption in the form of the distribution, shifting the mode toward shorter IRTs. With repeated administration of the drug, the distributions again were peaked in the region of the IRT criterion, but very short (0–4 sec) IRTs ("bursts") persisted. Upon withdrawal of Δ⁹-THC, IRTs longer than the minimum required generally became more frequent. Similar effects were observed with Monkeys 501 and 504 during and after chronic administration of 0.25 mg/kg Δ⁹-THC.

Initially, when administration of the drug vehicle replaced daily injections of Δ⁹-THC (points under V in Figures 2 and 3) response rate during the RI component of the multiple schedule decreased for all monkeys. The frequency of pellet delivery during either component was greatly decreased only for Monkey 519 as a result of this disruption in responding, although Monkey 501's pellet frequency was moderately reduced. All other monkeys continued to produce pellets with frequencies comparable to baseline conditions. Responding recovered during the RI component graudally, if at all, following removal of Δ⁹-THC. Response rates in the RI component during daily administration of the vehicle appeared to return toward baseline levels more rapidly and to a greater degree following chronic treatment with 0.25 mg/kg Δ⁹-THC than following chronic treatment with 1.00 mg/kg, although this difference was not large.

DISCUSSION

Under the procedure used in the present study the IRT and RI schedules controlled distinctly different rates and temporal patterns of lever pressing, but resulted in reasonably similar interpellet distributions. Administration of Δ⁹-

THC initially produced either complete suppression of responding (Monkeys 501, 509, and 519) or suppression of high rates maintained by the RI schedule and disruption of spaced-responding under the IRT>28-sec schedule. All of these initial effects produced some degree of reinforcement loss, and tolerance developed to these effects in every animal. The rate of tolerance development, however, did not seem to be related to the degree of reinforcement loss in any consistent manner, thus lending at best only qualitative support to Ferraro's hypothesis.

Further administration of Δ^9-THC enhanced responding in some animals under both the IRT>28-sec and the RI component. A "cost" analysis of tolerance would predict that this rate enhancement should dissipate under the IRT schedule, but not under the RI schedule, since only in the former is rate of reinforcement diminished as a result of this effect. The data from the present study do not entirely bear out this prediction. While most subjects' RI response rates remained clearly elevated throughout the chronic series, there was one case in which this did not occur. Monkey 509, who showed elevated RI response rates early in the chronic series, recovered baseline responding before termination of the series.

Elevated response rates during the IRT component did diminish with repeated administration of Δ^9-THC, although none showed complete recovery, i.e., only partial tolerance was observed. These results may also seem at first incompatible with the hypothesis. Closer examination of the data, however, reveals that these findings are not completely inconsistent with the view that reinforcement loss plays an important role in tolerance development. Consider the IRT distributions in Fig. 4. Early in the chronic series, administration of Δ^9-THC elevated response rates by increasing the frequency of short and moderate length IRTs, decreasing the frequency of reinforced IRTs. Virtually complete tolerance developed to the increased frequency of moderate length (4–20 sec) IRTs (Compare rows 2 and 3 with row 1 in Fig. 4.), but did not develop as completely to the increased frequency of very short (less than 4 sec) ones. Thus, response-rate increases that were evident at the end of the chronic series resulted from a mixture of both reinforced and very short IRTs. "Cost" hypotheses predict that those disruptions which most severely reduce reinforcement frequency are those to which tolerance is more likely to develop, and the differential effects of chronic THC on very short and moderate length IRTs in the present study are consistent with such a position. Occasional moderate length IRTs produce a much greater reduction in reinforcement frequency than do very short IRTs. The drug's differential effects on moderate length vs very short IRTs calls into question the use of average response rate as a measure of tolerance development when tolerance is viewed as a behavioral adaptation to a drug's (adverse) effects. Reinforcement rate might be a better measure, since it does not by definition restrict the possible adaptations but rather places emphasis on the functional effect of such adaptations.

All animals showed substantial decreases in response rate during the RI component when vehicle was substituted for the drug. This "withdrawal" effect is consistent with previous reports involving interval schedules of reinforcement [4] and deserves further analysis. The present data suggest a relationship between dose and the degree of "withdrawal-induced" suppression, but methodological confoundings in the present study unfortunately prohibit further discussion. The present findings also suggest a possible schedule and/or rate-dependent nature of this withdrawal effect since only the higher rates of responding engendered by the RI schedule were greatly disrupted upon termination of Δ^9-THC injections.

The consistency of the present results obtained in squirrel monkeys with those obtained with other species (cf. [4, 5, 8, 9, 13, 14]) serve as an impressive display of interspecies generality, and the present results generally support a "cost" notion of tolerance development, but also point out some clear exceptions. Obviously a more formal statement of the hypothesis must include variables which will account for these exceptions.

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