MORPHINE TOLERANCE AS A FUNCTION OF RATIO SCHEDULE: RESPONSE REQUIREMENT OR UNIT PRICE?

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Key pecking by 3 pigeons was maintained by a multiple fixed-ratio 10, fixed-ratio 30, fixed-ratio 90 schedule of food presentation. Components differed with respect to amount of reinforcement, such that the unit price was 10 responses per 1-s access to food. Acute administration of morphine, l-methadone, and cocaine dose-dependently decreased overall response rates in each of the components. When a rate decreasing dose of morphine was administered daily, tolerance, as measured by an increase in the dose that reduced response rates to 50% of control (i.e., the ED_{50} value), developed in each of the components; however, the degree of tolerance was smallest in the fixed-ratio 90 component (i.e., the ED_{50} value increased the least). When the l-methadone dose-effect curve was redetermined during the chronic morphine phase, the degree of cross-tolerance conferred to l-methadone was similar across components, suggesting that behavioral variables may not influence the degree of cross-tolerance between opioids. During the chronic phase, the cocaine dose-effect curve shifted to the right for 2 pigeons and to the left for 1 pigeon, which is consistent with predictions based on the lack of pharmacological similarity between morphine and cocaine. When the morphine, l-methadone, and cocaine dose-effect curves were redetermined after chronic morphine administration ended, the morphine and l-methadone ED_{50}s replicated those obtained prior to chronic morphine administration. The morphine data suggest that the fixed-ratio value (i.e., the absolute output) determines the degree of tolerance and not the unit price.

Key words: morphine, fixed-ratio schedule, amount of reinforcement, tolerance, unit price, key peck, pigeons

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Repeated administration of some drugs may lead to the development of tolerance to their behavioral effects. Tolerance occurs when the

initial effect of a drug diminishes and larger doses are required to produce the initial effect. In terms of a graph of the relation between drug dose and behavioral effect, the peak of the curve shifts to the right. A variety of environmental and behavioral variables can affect whether or not, and the degree to which, tolerance develops to the behavioral effects of drugs (see Goudie & Emmett-Oglesby, 1989). One variable that can influence tolerance to the effects of drugs on operant behavior is the schedule of reinforcement under which the behavior is maintained. Under multiple ratio schedules of food presentation, several investigators have reported that the degree of tolerance to the effects of a number of drugs on response rate was an inverse function of ratio parameter; that is, the response requirement. For example, Hoffman, Branch, and Sizemore (1987) exposed pigeons to a multiple schedule in which the components differed with respect to the fixed-ratio (FR) schedule. Tolerance to the response-rate-decreasing effects of cocaine developed in the smaller-value components (i.e., FR 5 and FR 25), but did not develop, or developed to a lesser extent, in the large-value components

(i.e., FR 50 or FR 125). A similar relation was obtained between FR parameter and degree of tolerance to other drugs (e.g., morphine, (-)-nantradol, and clonidine), with other species (e.g., squirrel monkeys and rats) and when responding was maintained under multiple random-ratio schedules (Branch, 1990; Hughes & Branch, 1991; Nickel & Poling, 1990; Smith, 1986b; 1990).

It is unlikely that the differential effects of response requirement on tolerance, typically found in multiple schedules, are related to differences in reinforcement rate as the degree of tolerance to the effects of cocaine does not depend upon the interreinforcement intervals arranged in fixed- and random-interval schedules (Branch, 1990; Schama & Branch, 1989). It is possible, however, that the different degrees of tolerance observed under FR schedules in multiple schedules may reflect control by the amount of ''effort'' or ''behavioral cost'' required for reinforcement (see Hoffman et al., 1987). That is, tolerance may be less likely to develop under conditions in which larger amounts of effort are required.

In each of the studies in which ratio-schedule-dependent tolerance was found, the number of required responses was varied while the amount of food presented per reinforcement remained constant. In behavioral-economic terms, such manipulations change the *unit price* of food. Unit price is a ratio specifying the cost (e.g., effort or monetary) expended per unit of a commodity (e.g, a reinforcer) (see Hursh, Raslear, Shurtleff, Bauman, & Simmon, 1988). Under ratio schedules, effort is a product of the number of required responses and the force required to emit the response, such that unit price = responses × force/reinforcement amount. Note that a given unit price can be constructed by combining any of several values of each of its constituents. Thus, according to behavioral-economic theory, unit price is a more fundamental controlling variable than each of its constituents (Collier, Johnson, Hill, & Kaufman, 1986; Hursh, 1980, 1984; Hursh et al., 1988). Indeed, several investigators have successfully applied the concept of unit price to characterize effects of manipulations of response requirement and/or reinforcement amount with both food and drug reinforcers (e.g., Bickel, DeGrandpre, Higgins, & Hughes,

1990; Bickel, DeGrandpre, Hughes, & Higgins, 1991; Collier et al., 1986; DeGrandpre, Bickel, Hughes, Layng, & Badger, 1993; Hursh & Winger, 1995; Hursh et al., 1988). It should be noted, however, that when manipulating unit price, other researchers have found that behavior is controlled more by either the response requirement or the reinforcement amount (e.g., English, Rowlett, & Woolverton, 1995; Foster & Hackenberg, 2004).

The treatment of response requirement and reinforcement amount as constituents of a more fundamental controlling variable (unit price) raises questions as to the nature of control over tolerance by response requirement. In particular, it is difficult to determine whether differential tolerance as a function of the ratio is controlled by the number of responses required for reinforcement per se or by the number of responses per unit of reinforcement (i.e., by unit price). To address this issue, key pecking by pigeons under a multiple FR 10 FR 30 FR 90 schedule of food presentation was examined in the present study. The amount of reinforcement, seconds access to grain, was adjusted proportionally across the three components such that the nominal unit price was 10 responses per 1-s access to grain. Dose-effect curves for morphine given acutely were determined before and during a regimen in which a fixed dose of morphine was administered prior to daily experimental sessions. The logic of this approach is relatively straightforward: Differential tolerance across components, similar to that obtained previously, would suggest that response requirement controls the degree of tolerance development. An absence of differential tolerance across components, however, would suggest that unit price is a controlling variable in tolerance development.

In addition to examining the effects of response requirement on morphine tolerance with unit price held constant, the current study also examined whether or not the daily morphine regimen produced cross-tolerance to other drugs. Previous research indicated that tolerance to the rate-decreasing effects of morphine, after morphine was administered repeatedly, can result in cross-tolerance between morphine and *l*-methadone (pharmacologically similar to morphine) in pigeons (Craft, Picker, & Dykstra, 1989; Heifetz & McMillan, 1971), rats (Picker, Negus, & Powell,

1991; Young, Kapitsopoulos, & Makhay, 1991), and squirrel monkeys (Hughes, Picker, & Dykstra, 1995; Oliveto, Picker, & Dykstra, 1991), but typically does not result in cross-tolerance to the effects of drugs from other pharmacological classes (Brocco & McMillan, 1983; Foltin & Schuster, 1982; Hughes, Dykstra, & Picker, 1996; Sannerud et al., 1993; Sannerud & Young, 1986; Smith, 1978; Woolverton, Kandel, & Schuster, 1978). Therefore, in this experiment, dose-effect curves for *l*-methadone and cocaine (pharmacologically dissimilar to morphine) were determined before and during the regimen of daily morphine administration.

METHOD

Subjects

Three experimentally naive adult female White Carneau pigeons (*Columba livia*) served as subjects. Each pigeon was housed individually in a colony room (12:12 hr light/dark cycle) with free access to water and health grit throughout the experiment. Pigeons were maintained at 80% of their free-feeding weights through feedings of grain immediately after experimental sessions. Once food deprived, Pigeons 9469, 9130, and 9139 weighed 400, 415, and 468 g, respectively.

Apparatus

Experimental sessions were conducted in three identical operant-conditioning chambers for pigeons with an interior dimension measuring 35.0 cm deep by 30.5 cm wide by 36.0 cm high. Three response keys, 2.5 cm in diameter, were located in a horizontal row on the front wall, 8.5 cm from each other (center to center), and each side key was 9.0 cm from a side wall. Only the middle key was operative, and it could be transilluminated by a green, red, or yellow light. A 1.2-W white houselight was located 6.5 cm above the middle response key. Pecks on the key with a force exceeding 0.20 N operated a microswitch and were counted as responses. A 5.0- by 6.0-cm opening, through which grain could be obtained, was centered on the front wall, 11.0 cm below the middle response key. Reinforcement consisted of timed access to mixed grain from a solenoid-operated food magazine raised behind the opening. Each chamber was

equipped with a ventilation fan, and the chambers were located in a room with white noise continuously present. Contingencies were programmed and data were collected by MED-PC[TM], Version 2.0 software (Georgia, VT) and a MED Associates interface located in a different room.

Behavioral Procedure

Following adaptation and magazine training, key pecking was shaped through differential reinforcement of successive approximations in the presence of a red keylight. The houselight was illuminated whenever the keylight was on. Key pecking then was reinforced according to an FR 1 schedule for one session each in the presence of a green and a yellow keylight. Then a three-component, multiple schedule was implemented, and the ratio value in each component was raised gradually across sessions until the terminal schedule values were FR 10 in the presence of the red keylight, FR 30 in the presence of the yellow keylight, and FR 90 in the presence of the green keylight. Each component was preceded by a 1-min time-out, during which the lights were out and the key was inoperative, and consisted of either four presentations of the FR or the lapse of a time limit. Each session consisted of two blocks of the three components; within each block, components were presented randomly.

During these initial sessions, reinforcement consisted of 3.5-s presentation of grain in the food hopper. During reinforcement, the houselight and keylight were turned off and the hopper was illuminated. After response rates were stable, the reinforcement durations were changed to 1.5 s and 9.5 s in the FR 10 and FR 90 components, respectively. Epstein (1981) showed that the latency for pigeons to start eating from the food hopper after completing a ratio is approximately 0.5 s. Therefore, the reinforcement durations in the present experiment were assumed to result in 1, 3, and 9 s of eating time per ratio during the FR 10, FR 30, and FR 90 components, respectively. Thus the nominal unit price in each component was 10 responses per 1-s access to grain. Performance was considered stable after response rates in seven consecutive sessions showed minimal variability (i.e., range of response rates was within $\pm$ 15% of

mean) and there were no consistent trends in response rates as determined by visual examination of the daily plots.

After response rates again were stable, the component durations were adjusted so that if the pigeon did not complete the four FRs within the allotted time, the 1-min timeout occurred and the next randomly selected component started. This was done so that the component would change in the event that a dose of a drug completely suppressed response rates, and therefore all of the components still would be experienced within the session. The component durations were 2 min, 4 min, and 15 min for the FR 10, FR 30, and FR 90 components, respectively. Therefore, the maximum length of a session was 48 min. These values were chosen to be at least twice as long as the longest duration of a component observed after stable responding had been established and before drugs were administered. Sessions were conducted at approximately the same time of day 5 days a week during the prechronic and postchronic phases and 7 days a week during the chronic phase.

Pharmacological Procedure

Injections were administered i.m. in the left or right pectoral muscle (site alternated from injection to injection). *l*-Methadone or morphine was administered 29 min prior to sessions (i.e., 30 min prior to the start of the first component), and cocaine was administered 4 min prior to sessions (i.e., 5 min prior to the start of the first component). The range of doses for each drug was such that at least one dose produced no decrease in response rates in any component and at least one dose decreased response rates in each component to less than 10% of response rates obtained when the drug vehicle (i.e., saline) was injected prior to the session (control rates). Two determinations of the dose-effect curve for each drug were completed. All doses of a given drug were administered in a random order at least once before the second determination of that drug was completed. Both determinations of the dose-effect curve for a particular drug were completed before the next drug was administered.

Prechronic morphine administration. Drug injections began after the terminal schedule values were reached and response rates were stable. Drugs generally were administered on Tuesdays and Fridays and the drug vehicle, saline, was administered on occasional Thursdays. Dose-effect curves were determined in the following order: cocaine, morphine, and *l*-methadone according to the procedure described above. The duration of the prechronic phase was 132 to 135 sessions.

Chronic morphine administration. After at least seven consecutive sessions of stable responding following the determination of the prechronic dose-effect curves, saline was administered prior to at least three consecutive sessions. Then a dose of morphine that had suppressed response rates to less than 10% of control rates in each component was administered before every session. The chronic dose of morphine was 30.0 mg/kg for Pigeons 9469 and 9130 and 5.6 mg/kg for Pigeon 9139. After at least 30 days of administration of the chronic dose of morphine, saline was administered before a selected session. Then dose-effect curves were redetermined in the following order: morphine, *l*-methadone, cocaine, and morphine. Therefore, there were two determinations of the morphine dose-effect curve and one determination of each of the *l*-methadone and cocaine dose-effect curves. These dose-effect curves were determined by substituting other doses of a drug or saline for the chronic dose of morphine approximately once per week. Intervening sessions were preceded by injections of the chronic dose of morphine. The duration of the chronic morphine phase was 201 to 229 days.

Postchronic morphine administration. After at least seven consecutive sessions of stable responding following the termination of daily morphine administrations, dose-effect curves were redetermined in the following order: morphine, *l*-methadone, and cocaine according to the regimen described above. The duration of the postchronic phase was 136 to 142 sessions.

Drugs

l-Methadone hydrochloride (Eli Lilly and Co., Indianapolis, IN), morphine sulfate, and cocaine hydrochloride (provided by the National Institute on Drug Abuse, Rockville, MD) were dissolved in sterile 0.9% saline. Doses are expressed in terms of the salt. Drugs were administered (i.m.) in a constant injection volume of 1.0 ml/kg body weight (as

determined by the weight of the pigeon before the session).

Amount of Grain Consumed

After all the dose-effect curves were determined in the chronic and postchronic phases of the experiment, the amount of grain (g) consumed during each type of FR component was measured for each pigeon.[1] During the chronic phase, the amount of grain consumed was measured twice in each component for each pigeon, and during the postchronic phase, it was measured twice in each component for Pigeon 9469 and, due to time constraints, only once in each component for Pigeons 9130 and 9139. Prior to selected sessions, the hoppers were removed from the chamber, and the grain was weighed and replaced in the hopper. The multiple schedule was programmed to begin in a particular component, and after the first component was completed, the sessions ended. The hoppers again were removed from the chambers, and the grain was weighed.

The amount of grain consumed per FR completed was calculated by dividing the total amount of grain consumed during one component by 4 (the number of FRs per component).

Therefore, the unit price was calculated two ways: The FR value divided by the seconds access to grain, and the FR value divided by the amount of grain (g) consumed.

Data Analysis

Overall response rates for each FR value were calculated for individual pigeons by dividing the number of responses that occurred during each component by the time spent in that component minus the total reinforcement time. There were no consistent differences in response rates across the two blocks of the session, and therefore, response rates for each FR value were averaged across blocks. For each drug, separate ''control rates'' were determined for each FR value;

control rates were the response rates from the three or four sessions before which saline was administered during the determination of a particular drug's dose-effect curve in the prechronic phase (see Table 1). For the dose-effect curves from each phase, the mean response rate from the session after a dose of a drug was administered was expressed as a percentage of that drug's control rates.

Dose-effect curves for response rates from the FR 10, FR 30, and FR 90 components were obtained for individual pigeons during the prechronic, chronic, and postchronic phases. From these curves, the dose of each drug that decreased response rates to 50% of control rates (i.e., the ED_{50} value) in each component was estimated for individual pigeons by log-linear interpolation of the descending portion of the dose-effect curves that included no more than one point above 80% of control rates, one point below 20% of control rates, and all intermediate points. For the conditions in which doses were administered twice, the ED_{50} value was interpolated using the mean dose-effect curve. A tolerance ratio was calculated for individual pigeons by dividing the ED_{50} value of the dose-effect curve obtained during the chronic phase by the ED_{50} value of the dose-effect curve obtained during the prechronic phase. Therefore, a value greater than 1.0 indicated a shift to the right in the dose-effect curve, and a value less than 1.0 indicated a shift to the left in the dose-effect curve. Thus the unit of magnitude of tolerance was the change in the ED_{50} values.

RESULTS

Control Performance

Patterns of responding characteristic of FR schedules were observed for each pigeon: A pause of a consistent length occurred after grain delivery, followed by an abrupt transition to a steady rate of responding (Ferster & Skinner, 1957). Table 1 presents the mean overall response rates during the FR 10, FR 30, and FR 90 components for the individual pigeons from the seven noninjection baseline sessions at the beginning of each phase and from subsequent sessions prior to which saline was administered during each phase. During baseline sessions, response rates for all pigeons tended to be lowest in the FR 90 component.

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[1] We gratefully acknowledge Dr. Steven R. Hursh's suggestion of measuring the amount of grain (g) consumed during the components. Unfortunately, the suggestion was made after the chronic phase had begun, and therefore, we do not have data from the prechronic phase. We are using the data from the postchronic phase as nondrug control data.

Table 1

Mean overall responses rates (responses per minute) for individual pigeons during the FR 10, FR 30, and FR 90 components of the multiple schedule from n baseline sessions (no injections given) at the beginning of the pre- and postchronic phases and from n saline control sessions (a saline injection before the session) during the prechronic, chronic, and postchronic phases. The range of response rates is shown in parentheses. The order of drug administration was morphine, *l*-methadone, cocaine, except during the prechronic phase when the order was cocaine, morphine, *l*-methadone.

		Pigeon 9469				Pigeon 9130				Pigeon 9139		
	n	FR 10	FR 30	FR 90	n	FR 10	FR 30	FR 90	n	FR 10	FR 30	FR 90
Prechronic												
Baseline	7	159.64	175.77	152.27	7	158.27	160.11	121.20	7	151.91	153.64	77.67
		(154–167)	(174–187)	(139–162)		(152–163)	(145–169)	(110–129)		(135–165)	(142–167)	(66–85)
Test-Drug												
Morphine	3	139.10	149.49	166.11	4	161.98	174.80	161.49	4	141.06	133.87	94.93
		(132–143)	(129–170)	(150–176)		(156–170)	(165–187)	(157–170)		(126–165)	(128–140)	(83–107)
l-Methadone	3	135.82	143.27	168.16	3	174.64	186.12	174.11	3	151.66	141.12	89.68
		(134–137)	(142–144)	(164–172)		(170–177)	(173–195)	(157–183)		(134–163)	(137–147)	(89–91)
Cocaine	4	161.77	177.07	158.71	3	169.52	179.77	140.93	3	176.6	175.93	88.12
		(156–167)	(162–185)	(153–168)		(165–174)	(172–185)	(123–161)		(161–205)	(165–188)	(86–95)
Chronic												
Test-Drug												
Morphine	2	151.99	167.24	155.11	2	151.89	157.08	144.50	3	148.58	142.48	116.02
		(138–166)	(167–168)	(152–158)		(145–158)	(155–160)	(137–152)		(126–162)	(127–161)	(98–139)
l-Methadone	1	159.11	162.33	147.55	1	149.71	174.14	124.14	1	163.82	125.45	102.76
Cocaine	1	159.68	161.11	140.19	1	129.13	145.79	175.88	1	118.11	133.05	94.06
Postchronic												
Baseline	7	168.24	174.62	161.06	7	180.13	195.59	144.48	7	138.54	129.42	96.64
		(161–176)	(158–185)	(152–167)		(167–188)	(185–204)	(127–164)		(103–167)	(95–145)	(80–111)
Test-Drug												
Morphine	3	156.73	169.12	148.45	3	168.73	185.10	136.21	2	166.63	152.69	162.65
		(147–162)	(161–180)	(139–159)		(161–176)	(180–188)	(98–152)		(160–173)	(151–154)	(151–174)
l-Methadone	3	168.40	184.38	161.64	2	162.15	160.99	106.75	3	140.20	139.47	129.93
		(163–172)	(180–189)	(159–163)		(156–168)	(153–169)	(97–117)		(125–169)	(129–145)	(114–147)
Cocaine	2	150.41	185.92	149.66	2	169.29	164.48	141.15	3	179.94	126.87	122.43
		(149–152)	(177–195)	(143–156)		(159–179)	(164–165)	(136–146)		(159–204)	(121–132)	(107–136)

Over the time course of the experiment (approximately 500 sessions), there were no consistent changes in response rates. A comparison of baseline response rates during the prechronic and during the chronic phases (see Table 1) reveals that response rates changed by an average of 12.54% (minimum = 0.65; maximum = 24.42) across pigeons.

Prechronic Phase

Figures 1, 2, and 3 show that prechronic morphine, *l*-methadone, and cocaine dose-dependently decreased response rates (unfilled circles) for all pigeons. Overall, *l*-methadone was more potent than morphine in producing rate-decreasing effects for all pigeons (see ED_{50} values in Table 2). Also, the response rates of Pigeon 9139 generally were more sensitive to the rate-decreasing effects of morphine and *l*-methadone than the rates of

the other pigeons (see Table 2). Across FR components, response rates were equally sensitive to the rate-decreasing effects of morphine and *l*-methadone in each of the components for Pigeon 9469; as seen in Table 2, ED_{50} values differed from each other by less than approximately a third. For the other 2 pigeons, response rates in the FR 90 component were more sensitive to the decreasing effects of morphine and *l*-methadone than the rates in the other two components. For these pigeons, the ED_{50} value in the FR 10 component was close to double that in the FR 90 component. For all pigeons, response rates were equally sensitive to the decreasing effects of cocaine in each component.

Chronic Morphine Administration

After at least 30 daily administrations of the chronic dose of morphine, response rates had
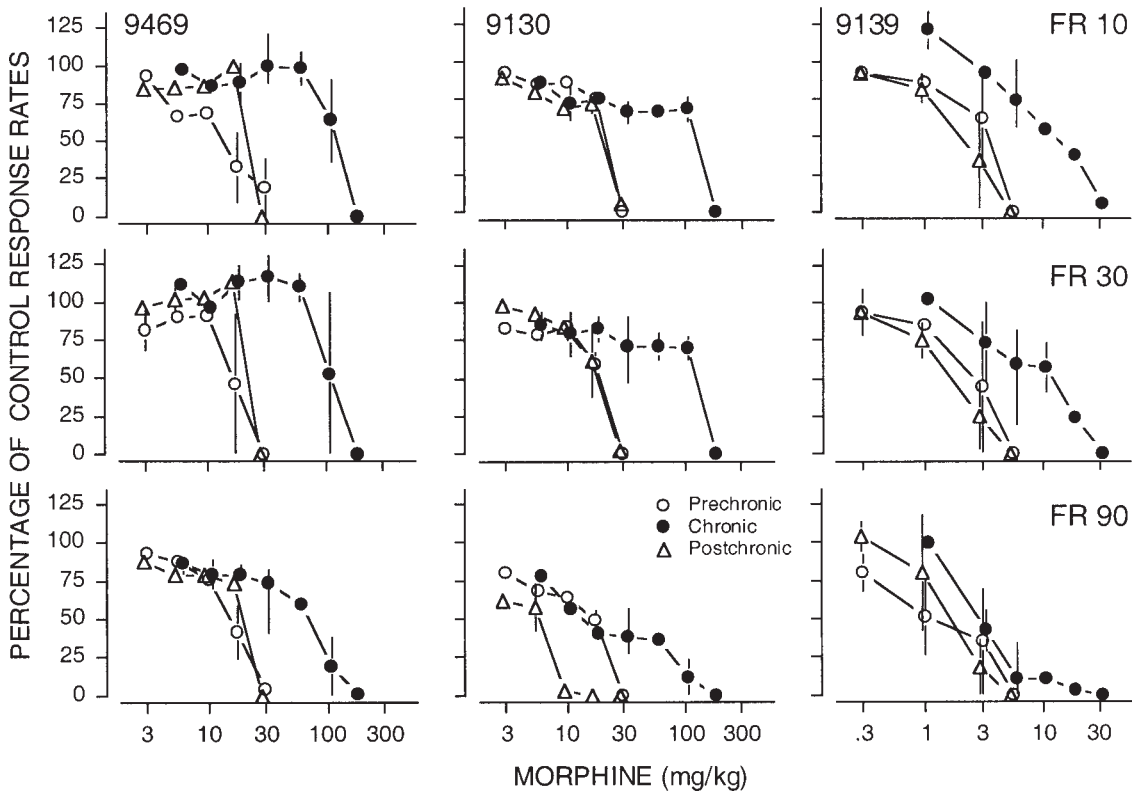
Fig. 1.   Mean overall response rates expressed as a percentage of response rates from sessions during which saline was administered as a function of dose of morphine for Pigeons 9469 (left panels), 9130 (middle panels), and 9139 (right panels) during the FR 10 component (top row), FR 30 component (middle row), and FR 90 component (bottom row). Note that the range of the *x* axis is different for Pigeon 9139 than for the other 2 pigeons. Open circles represent data from the prechronic phase; filled circles represent data from the chronic phase; open triangles represent data from the postchronic phase. Data points are a mean of two determinations; except, during the chronic phase, points above 30.0 mg/kg morphine for Pigeons 9469 and 9130 and 5.6 mg/kg morphine for Pigeon 9139 are means from 13 to 15 sessions prior to which those chronic doses were administered that preceded a session in which the effects of another dose of morphine or saline were determined. Vertical lines represent the range. In each graph, the dose-effect curves have been displaced slightly on the *x* axis for clarity.

increased and were stable in each component for each pigeon. For Pigeon 9469, response rates now were above 80% of prechronic control rates (i.e., during the morphine dose-effect curve during the prechronic phase) in the FR 10 and FR 30 components and were 74% of prechronic control rates in the FR 90 component (data not shown). For the other 2 pigeons, response rates were an average of 61% of prechronic control rates in the FR 10 and FR 30 components. Response rates in the FR 90 component, however, were only 36% and 12% of prechronic control rates for Pigeons 9139 and 9130, respectively (data not shown). The overall degree of tolerance remained fairly consistent throughout the

chronic phase (see range bars above chronic dose in Figure 1).

Figure 1 shows that tolerance developed to the rate-decreasing effects of morphine in each component; that is, the dose-effect curves shifted to the right for all pigeons. The degree of tolerance, however, varied across components. For Pigeon 9469, the chronic ED_{50} values were more than 6 times greater than the prechronic ED_{50} values in the FR 10 and in the FR 30 components. For Pigeons 9130 and 9139, the chronic ED_{50} values were between 3.5 and 4.5 times greater than the ED_{50} values in the FR 10 and FR 30 components. More important, for each pigeon, the degree of tolerance was smallest in the FR 90 component;
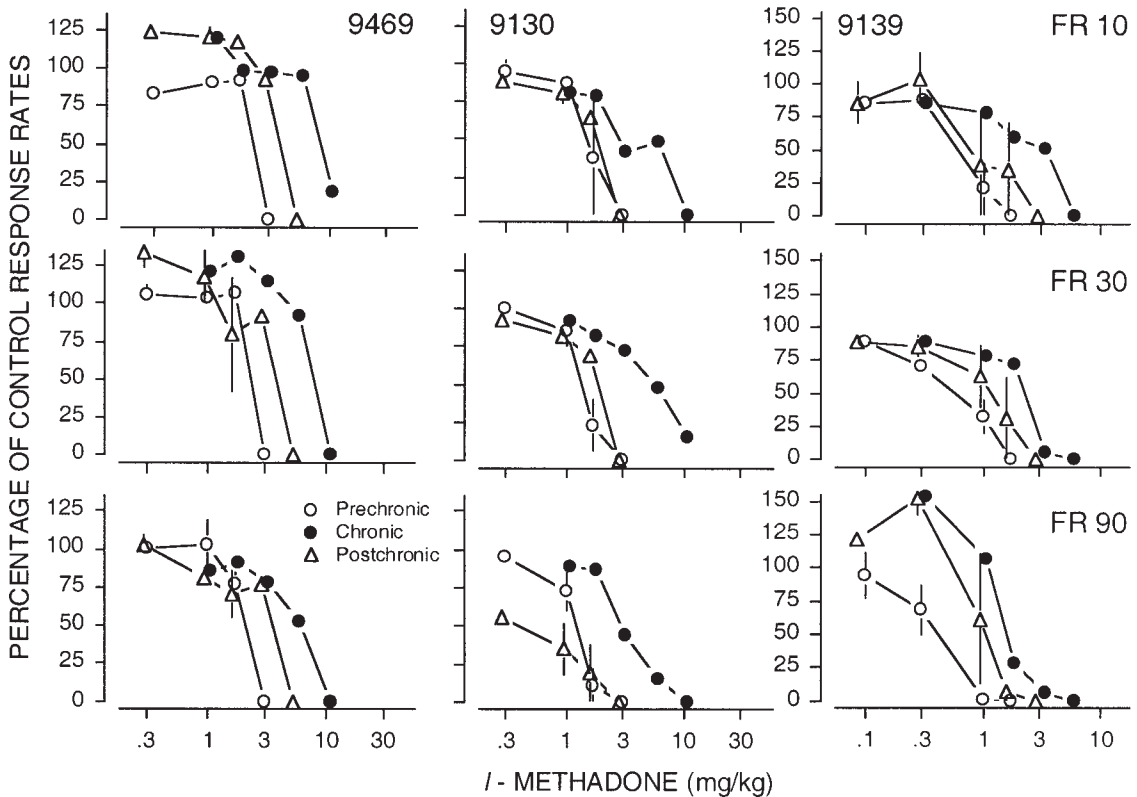
Fig. 2.   Mean overall response rates expressed as a percentage of response rates from sessions during which saline was administered as a function of dose of *l*-methadone for Pigeons 9469 (left panels), 9130 (middle panels), and 9139 (right panels) during the FR 10 component (top row), FR 30 component (middle row), and FR 90 component (bottom row). Data points are a mean of two determinations; except, during the chronic phase, doses were administered only once. Plotting conventions are the same as Figure 1.

the shifts in the ED_{50} values were less than half of those observed in the FR 10 component (see Table 2).

The top panel of Figure 4 shows the degree of tolerance to the rate-decreasing effects of morphine in each of the components represented as the log ratio between the ED_{50} value obtained during the chronic phase and the ED_{50} value obtained during the prechronic phase (i.e., the tolerance ratio). A value of 1 indicates no tolerance; values greater than 1 indicate a shift to the right of the dose-effect curve; values less than 1 indicate a shift to the left of the dose-effect curve. For each pigeon, the tolerance ratio was smallest in the FR 90 component. The tolerance ratios from the FR 10 (Pigeons 9469 and 9139) and the FR 30 (Pigeon 9130) components are nearly twice that of the tolerance ratio in the FR 90 component.

Figures 2 and 4 and Table 2 show that during repeated administrations of morphine, the dose-effect curves for *l*-methadone shifted to the right of the prechronic *l*-methadone dose-effect curves for each pigeon; the chronic ED_{50} values were between 2 to 5 times greater than the prechronic ED_{50} values. In contrast to the findings with morphine, the degree of the shift was comparable across components for each pigeon.

Figures 3 and 4 and Table 2 show that during repeated administrations of morphine, the dose-effect curves for cocaine shifted relative to prechronic dose-effect curves for each pigeon, and the degree of the shift did not depend on the component. For Pigeons 9469 and 9130, the cocaine dose-effect curves in each component shifted to the right; the chronic ED_{50} values were approximately 2 times greater than the prechronic ED_{50} values.
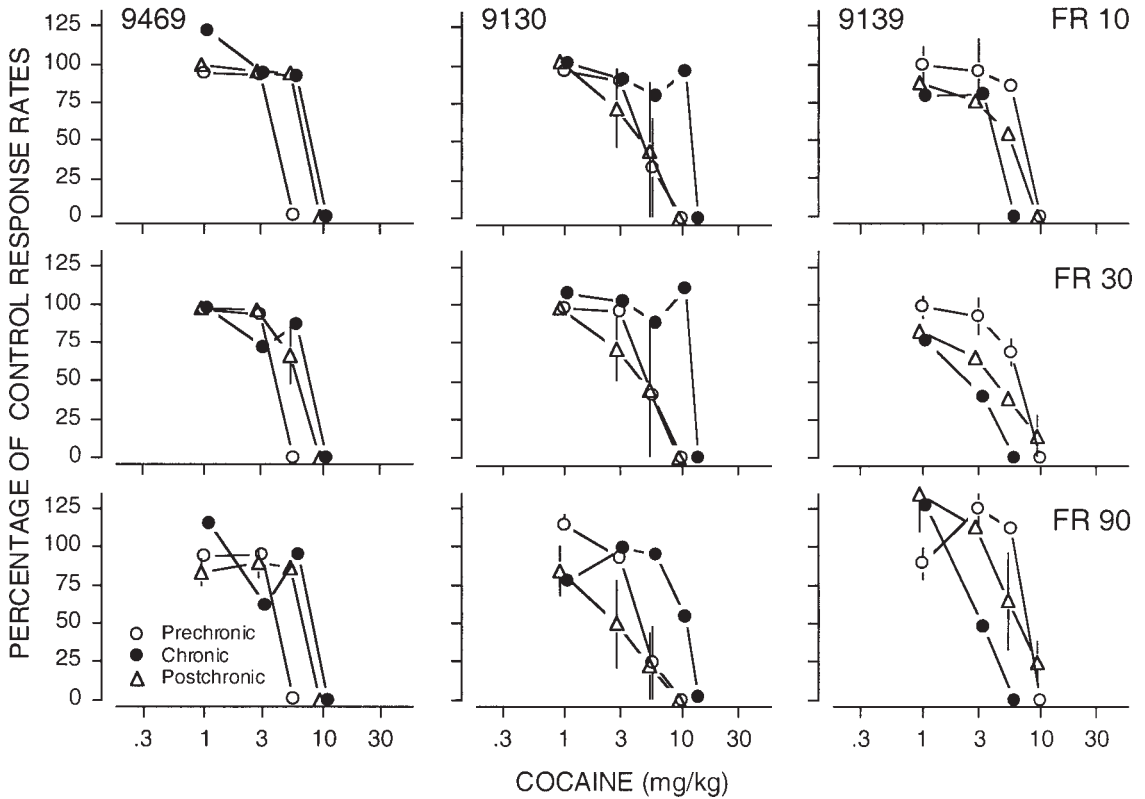
Fig. 3.   Mean overall response rates expressed as a percentage of response rates from sessions during which saline was administered as a function of dose of cocaine for Pigeons 9469 (left panels), 9130 (middle panels), and 9139 (right panels) during the FR 10 component (top row), FR 30 component (middle row), and FR 90 component (bottom row). Data points are a mean of two determinations; except, during the chronic phase, doses were administered only once. Plotting conventions are the same as Figure 1.

Table 2

Individual ED$_{50}$ values (mg/kg) for each drug for individual pigeons during the FR 10, FR 30, and FR 90 components during the prechronic, chronic, and postchronic phases.

| Drug phase	Pigeon 9469			Pigeon 9130			Pigeon 9139		
	FR 10	FR 30	FR 90	FR 10	FR 30	FR 90	FR 10	FR 30	FR 90
Morphine									
Prechronic	11.86	16.53	13.60	18.22	16.90	10.44	2.52	1.93	1.07
Chronic	102.84	102.70	52.10	63.59	75.00	16.63	10.54	7.29	2.56
Postchronic	22.80	23.63	17.60	15.60	17.20	3.60	2.02	1.43	1.70
l-Methadone									
Prechronic	2.20	2.29	1.92	1.54	1.44	0.99	0.61	0.44	0.34
Chronic	7.88	7.30	5.00	3.32	4.62	2.98	2.16	1.76	1.66
Postchronic	3.99	3.98	2.72	1.68	1.73	0.42	0.97	0.97	1.06
Cocaine									
Prechronic	4.01	4.01	4.04	4.89	5.23	4.79	7.11	5.80	7.73
Chronic	7.30	7.16	7.37	11.34	11.54	9.05	3.80	1.96	2.87
Postchronic	7.34	5.84	7.16	4.02	3.89	2.67	4.10	3.64	6.99
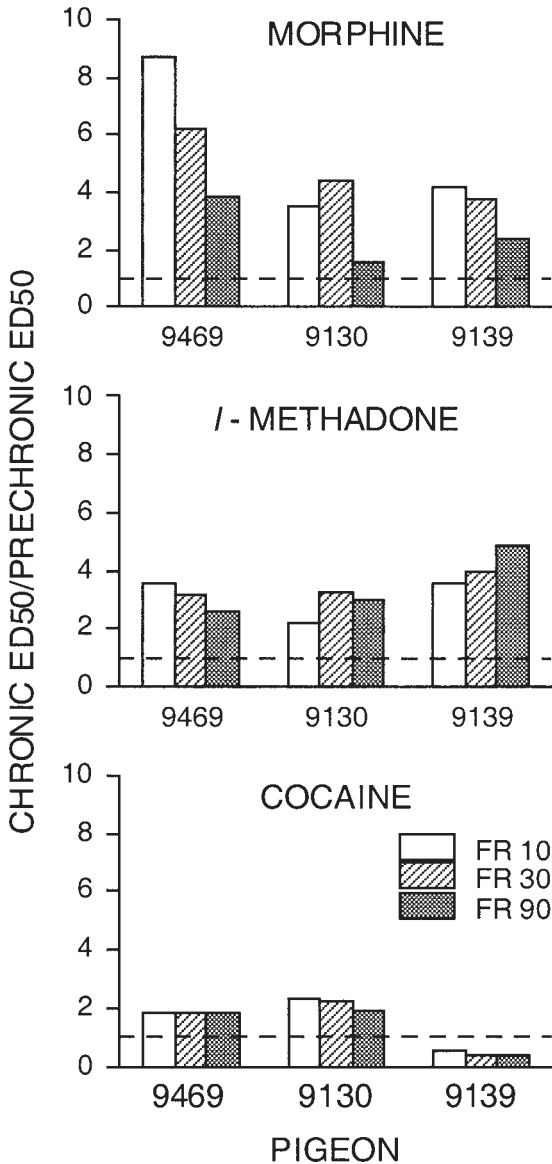
Fig. 4. The ratio between the ED_{50} value obtained during the chronic phase and the ED_{50} value obtained during the prechronic phase for morphine (top row), *l*-methadone (middle row), and cocaine (bottom row) during the FR 10 component (open bars), FR 30 component (striped bars), and FR 90 component (solid bars). The dashed line at 1.0 represents no change in the ED_{50} values during the chronic phase.

For Pigeon 9139, the cocaine dose-effect curves shifted to the left; the chronic ED_{50} values were approximately 0.33 to 0.5 of the prechronic ED_{50} values.

Postchronic Phase

After an average of 215 (201 to 229) days of morphine administration, injections prior to the sessions were terminated, and following at least 30 days of no injections and seven sessions of stable responding, dose-effect curves were redetermined. Figure 1 and Table 2 show that the morphine dose-effect curve usually shifted back in the direction of the prechronic dose-effect curve in each of the components. For Pigeon 9469, however, the postchronic ED_{50} value was almost twice that of the prechronic ED_{50} value in the FR 10 component, indicating that the curve remained shifted to the right. For Pigeon 9130, the postchronic ED_{50} value was approximately a third of the prechronic ED_{50} value in the FR 90 component, indicating that the curve now was shifted to the left of the one obtained before repeated administration of morphine.

Figure 2 and Table 2 show that the *l*-methadone dose-effect curves shifted back in the direction of the prechronic dose-effect curve in each of the components for each of the pigeons. For Pigeons 9469 and 9139, however, the postchronic *l*-methadone dose-effect curves remained shifted to the right of the prechronic dose-effect curves; the postchronic ED_{50} values were approximately 1.5 to 3 times greater than the prechronic ED_{50} values. For Pigeon 9130, the postchronic ED_{50} value was a little under half of the prechronic ED_{50} value in the FR 90 component, indicating that once again the postchronic curve was shifted to the left of the prechronic dose-effect curve.

Figure 3 and Table 2 show that the cocaine dose-effect curves shifted back in the direction of the prechronic dose-effect curves in all components for Pigeon 9130 and in the FR 90 component for Pigeon 9139. For Pigeon 9469, the postchronic cocaine dose-effect curves did not shift relative to the chronic dose-effect curve. For Pigeon 9139, the postchronic cocaine dose-effect curve remained shifted leftward relative to the prechronic dose-effect curve in the FR 10 and FR 30 components.

Amount of Grain Consumed

Table 3 shows the amount of grain that was consumed in each component in the chronic and the postchronic phases. Within a phase the values in each component were determined

Table 3

Mean amount of grain (g) consumed per reinforcer delivery and the obtained unit price (number of responses/amount of grain consumed) during the FR 10, FR 30, and FR 90 components for individual pigeons in each component during the chronic and postchronic phases.

Phase	Pigeon 9469			Pigeon 9130			Pigeon 9139		
	FR 10	FR 30	FR 90	FR 10	FR 30	FR 90	FR 10	FR 30	FR 90
Chronic									
Amount of grain	0.18	0.22	0.65	0.22	0.48	1.55	0.25	0.32	—[a]
Obtained unit price	55.60	136.40	138.50	45.40	62.50	58.10	40.00	93.80	—[a]
Amount of grain	0.12	0.18	0.78	0.20	0.58	1.40	0.15	0.22	—[a]
Obtained unit price	83.30	166.70	115.40	50.00	51.70	64.30	66.70	136.40	
Average									
Amount of grain	0.15	0.20	0.72	0.21	0.53	1.48	0.20	0.27	
Obtained unit price	66.70	150.00	125.00	47.60	56.60	60.80	50.00	111.10	
Postchronic									
Amount of grain	0.10	0.78	1.48	0.40	0.82	2.35	0.20	0.60	1.80
Obtained unit price	100.00	38.50	60.80	25.00	36.60	38.30	50.00	50.00	50.00
Amount of grain	0.30	0.62	2.32						
Obtained unit price	33.30	48.40	38.80						
Average									
Amount of grain	0.20	0.70	1.90	0.40	0.82	2.35	0.20	0.60	1.80
Obtained unit price	50.00	42.70	47.40	25.00	36.60	38.30	50.00	50.00	50.00

[a] This pigeon did not respond during the FR 90 component during the test sessions when the amount of food was measured.

in different sessions, which were separated by at least two sessions (see Method). The amount of grain consumed in a particular component typically varied across and within pigeons (when multiple measurements were obtained). Each pigeon ate more food during the postchronic phase than in the chronic phase (Pigeons 9469 and 9139 in the FR 10 component were the exception). In both phases, pigeons tended to eat close to 3 times as much grain when the hopper was presented for 9.5 s compared to when it was presented for 3.5 s. Therefore, the nominal unit prices are often similar in the FR 30 and FR 90 components. The nominal unit price in the FR 10 component tended to be lower than in the other two components across the pigeons. This occurred because the pigeons tended to eat less than 2 times as much grain when the hopper was presented for 3.5 s compared to when it was presented for 1.5 s.

DISCUSSION

In the present experiment, tolerance developed to the rate-decreasing effects of morphine in each of the FR components, in that the dose-effect curve shifted at least twofold to the right. Interestingly, the degree of tolerance was not uniform across components; the degree of tolerance was smallest in the FR 90 component. These data are consistent with those of Nickel and Poling (1990) who arranged a multiple schedule consisting of FR 5, FR 25, and FR 125 components and who also found that the degree of tolerance was greatest in the smaller-value component. These results also are consistent with other reports of differential tolerance development in multiple ratio schedules with various drugs and species (e.g., Branch, 1990; Hoffman et al., 1987; Hughes & Branch, 1991; Smith, 1986b, 1990). In Nickel and Poling's study, the unit price was unequal across the three FR sizes because the reinforcement amount was held constant while the FR size was increased. In the present study, equal unit prices were arranged by manipulating the size of the FR schedule and the duration of the grain hopper presentation. Given the similarity in the results of the present experiment to those of Nickel and Poling, the response requirement appears to be the crucial determining factor in the differential tolerance development. In addition, the results of the present experiment are consistent with those from a recent study (published since initial acceptance of this paper) showing that unit price did not predict the degree of tolerance to the effects of cocaine, but response requirement did (Yoon & Branch, 2004).

Although ratio-schedule dependent tolerance is a fairly robust effect, there are some conditions under which it does not develop. For example, Poling and his colleagues reported that the degree of tolerance was not inversely related to response requirement when FR schedules were arranged in a mixed schedule or when progressive-ratio schedules were used (Jarema, Macomber, LeSage, & Poling, 1999; Poling, Byrne, Christian, & LeSage, 2000; Poling, LeSage, Roe, & Schaefer, 1996). Poling and colleagues suggested that strong discriminative control over the responding, as found in a multiple schedule, may be a crucial variable in the development of differential tolerance.

In the present experiment, although less tolerance developed in the FR 90 component than in the smaller-value components for all pigeons, tolerance did develop in the FR 90 component and developed to a considerable degree for 1 pigeon. In some of the previous experiments, the degree of tolerance seen in the large-value component was much smaller (tolerance often did not develop) than in the smaller-value components (e.g., Hoffman et al., 1987; Hughes & Branch, 1991). Therefore, the development of tolerance in the FR 90 component in the present experiment may be evidence that the unit price modulated the degree of tolerance. The relation between the obtained unit prices and the degree of tolerance speaks to this issue. Although an equal nominal unit price was arranged across the components in the present experiment, the obtained unit price varied slightly across components during the chronic and post-chronic phases (see Table 3). In general, a more favorable unit price (i.e., smaller) was obtained in the FR 10 component than in the other two components. The obtained unit price tended to be similar in the FR 30 and FR 90 components. If unit price had influenced the degree of tolerance to the rate-decreasing effects of morphine, then the greatest degree of tolerance should have developed in the FR 10 component and comparable degrees of tolerance should have developed in the other two components. For 2 of the 3 pigeons, the greatest degree of tolerance was observed in the FR 10 component, whereas, for the other pigeon, the greatest degree of tolerance was observed in the FR 30 component. For each pigeon, however, the degree of tolerance that

developed was more similar across the FR 10 and FR 30 components than across the FR 30 and FR 90 components. Thus the degree of tolerance to the rate-decreasing effects of morphine was not predicted by the unit price alone.

Reinforcement amount may influence tolerance development. In the present experiment, however, it is not clear how much influence reinforcement amount alone had on the development of tolerance because conditions in which the FR remained constant and the reinforcement amount was varied systematically were not arranged. Under conditions in which the magnitude of negative reinforcement was manipulated (i.e., two intensities of shock), Smith (1991) found that tolerance to the rate-decreasing effects of clonidine in rats developed under the condition in which behavior was maintained by the avoidance of the higher shock intensity. Similarly, Smith (1986a) found that tolerance to the rate-decreasing effects of (+)-amphetamine developed in a component of a multiple schedule in which rats received a higher proportion of their daily earned reinforcers during baseline conditions. These findings suggest that a greater degree of tolerance will develop under conditions in which an absolute or relatively greater amount of reinforcement is obtained. In the present experiment, the largest absolute reinforcement amount was in the FR 90 component, although proportionally the amount of reinforcement across components was approximately the same. Therefore, if the degree of tolerance was modulated by reinforcement amount, the degree of tolerance to the rate-decreasing effects of morphine should have been either equivalent across components or largest in the FR 90 component. The degree of tolerance was smallest in the FR 90 component, however, suggesting that response requirement modulated the degree of tolerance to a greater extent than did reinforcement amount.

The influences of reinforcement amount and response requirement on tolerance development have been examined further in a more recent study (Stallings & Hughes, 1999). In this study, key pecking of pigeons was maintained by a multiple FR schedule of food reinforcement in which the FR schedule was either 30 or 90 and the reinforcement amount was either 3.5 s or 9.5 s. Therefore,

the nominal unit price in the four components was one of three values: approximately 3.33, 10, or 30. The effect of reinforcement amount was examined across two values with each of the FR values. After daily administration of morphine, tolerance developed to the rate-decreasing effects to a larger degree in the FR 30 components than in the FR 90 components. Interestingly, the amount of reinforcement appeared to affect the degree of tolerance in the FR 90 components as a greater degree of tolerance developed in the FR 90 component with 9.5-s reinforcer duration than in the FR 90 component with the 3.5-s reinforcer duration. These data also suggest that unit price per se was not the best predictor of the magnitude of tolerance.

In a couple of recent experiments, the basic unit-price model as used in the present experiment has been challenged. Both Madden, Bickel, and Jacobs (2000) and Foster and Hackenberg (2004) proposed that the basic unit-price model could be modified to include handling time and reinforcement delay as components of response effort; that is, the numerator of the equation. In their experiments, the modified unit-price model was a better predictor of their choice data, especially when comparable nominal unit prices were an arrangement of different FR values and amounts of reinforcement. This modified unit-price model can be applied to the data from the present study. The handling time of the reinforcer can be conceptualized as the time it took the pigeon to move its head from the key to the food hopper. Although we did not measure this directly in the present experiment, Epstein (1981) has shown that the average latency is 0.5 s. For each pigeon, the number of pecks they would have emitted in 0.5 s was determined based on their average control response rates during the chronic phase and added to the FR. The reinforcement delay was determined based on the average time for each pigeon to complete the ratio (based on the average control response rates during the chronic phase). When the modified model was used to determine unit prices for each pigeon, the prices increased as the FR increased across components (220, 572, 1,962 for the FR 10, FR 30, and FR 90 components, respectively, averaged across pigeons). Therefore, the differential degree of tolerance observed across the FR schedules

in the present study could be a result of the different unit prices. It should be noted, however, that in the modified model proposed by Madden et al. and Foster and Hackenberg, interreinforcement time was used as the measure of reinforcement delay. Interestingly, Schama and Branch (1989) and Branch (1990) found comparable degrees of tolerance to cocaine's rate-decreasing effects across different interreinforcement times arranged in multiple schedules of interval components. They suggested that comparable degrees of tolerance were found because only one response was required in each of the interval schedules; that is, a small ratio of responses to reinforcer was in effect when response rates were decreased by the drug.

Another variable that may influence the degree of tolerance is the absolute rates maintained by the different FR schedules; that is, perhaps more tolerance develops when control response rates are high. Just prior to the initiation of the chronic phase, however, response rates maintained by the FR 90 schedule were higher than or comparable to the rates maintained by the other FR schedules for 2 of the 3 pigeons. Yet for these 2 pigeons a greater degree of tolerance developed in the smaller-value components than in the large-value component. Therefore, the differential degree of tolerance that developed in the present study does not appear to be related clearly to absolute response rates.

Although absolute response rates were not a good predictor of the degree of tolerance that developed, the degree of disruption of responding by morphine during the prechronic phase may be. For each pigeon, but especially for 2 pigeons, morphine was more potent in decreasing response rates in the FR 90 component than in the other components, and less tolerance developed in the FR 90 component than in the other components. Young and Griffin (1990) also found that the degree of tolerance to the rate-decreasing effects of morphine that developed in rats responding under an FR schedule was inversely related to the extent of the decrease in response rates during the prechronic phase. Therefore, the ''strength'' of baseline responding, as indexed by the initial disruption by the drug, could be a predictor of tolerance development (cf., Hoffman et al., 1987). In

another experiment, pigeons were maintained at different levels of food deprivation (Hughes, Pitts, & Branch, 1996). The rate-decreasing effects of cocaine were attenuated and exacerbated when pigeons were maintained at a lower level or higher level of food deprivation, respectively. Even though the degree of deprivation influenced the initial effects of cocaine, comparable degrees of tolerance to cocaine developed when cocaine was administered repeatedly. Thus the strength of baseline responding may not necessarily be a good predictor of the degree of tolerance development.

In the present experiment, reinforcement amount was manipulated by altering the length of time the food hopper was presented. The mean amount of food (g) that the pigeons consumed during each component was proportional to the length of time the hopper was presented; that is, the amount of grain consumed to access time was a linear relation. These data are similar to those found by Epstein (1981) and by Foster and Hackenberg (2004) when they measured the grain consumed as a function of access time. Therefore, the smaller degree of tolerance observed in the FR 90 component was not a function of a smaller proportional amount of food consumed during 9-s access to the food hopper. These data also suggest that examination of unit price is possible in pigeons utilizing timed access to food as the reinforcer.

In the present experiment, the degree of cross-tolerance between morphine and *l*-methadone was examined. For each pigeon, the *l*-methadone dose-effect curve was shifted to the right in each of the components; that is, cross-tolerance between morphine and *l*-methadone developed in each of the components. These data are consistent with data from other experiments in which morphine was administered daily and tolerance developed to the rate-decreasing effects of morphine and cross-tolerance developed between morphine and *l*-methadone in pigeons (Craft et al., 1989; Heifetz & McMillan, 1971), in rats (Picker et al., 1991; Young et al., 1991), and in squirrel monkeys (Hughes et al., 1995; Oliveto et al., 1991).

The degree of cross-tolerance between the rate-decreasing effects of morphine and *l*-methadone was not dependent on the FR

schedule. For 2 of the pigeons the degree of cross-tolerance was comparable across components, and for 1 pigeon, in contrast to the data with morphine, the largest degree of cross-tolerance was observed in the FR 90 component. These data suggest that the degree of cross-tolerance that develops between opioids may not be modulated by behavioral variables such as ratio size. The extent to which behavioral variables can modulate the degree of cross-tolerance between drugs in similar pharmacological classes is unclear. In several experiments, however, cross-tolerance developed between drugs only in groups of rats that were administered the chronic drug prior to the session and did not develop in groups of rats that were administered the chronic drug after the session (i.e., behavioral tolerance) (Foltin & Schuster, 1982; Hughes et al., 1996; Sannerud et al., 1993; Woolverton et al., 1978). These findings suggest that the degree of cross-tolerance between drugs can depend on the temporal relation between the chronic drug administration and assessment of the behavioral effects. That is, the development of cross-tolerance can depend on experiencing the behavioral effect of the chronic drug during the chronic phase and having the opportunity to respond in the presence of the drug.

Effects of chronic morphine on the cocaine dose-effect curve were not consistent across pigeons. For 2 of the pigeons the cocaine dose-effect curve shifted to the right approximately twofold in each component, but for the 3rd pigeon the dose-effect curve shifted left approximately threefold in each component. Traditionally, behavioral tolerance that develops to a drug is not conferred to drugs outside of the chronic drug's pharmacological class (Brocco & McMillan, 1983; Hughes et al., 1996; Sannerud et al., 1993; Sannerud & Young, 1986). Interpretation of the effects of daily morphine administrations on the cocaine dose-effect curve in the present experiment is further complicated because the cocaine dose-effect curve did not return to prechronic levels in 2 of the 3 pigeons during the postchronic phase. These latter data suggest that the rate-decreasing effects of cocaine may vary over a period of 2 years.

In summary, the degree of tolerance to the rate-decreasing effects of morphine was dependent on the size of the FR schedule

maintaining responding; less tolerance developed in the large-ratio component than in the smaller-ratio components of the multiple schedule. Differential degrees of tolerance developed even though equivalent unit prices were arranged across components suggesting that response requirement or output is a crucial determinant of tolerance. In addition, behavioral cross-tolerance developed to the rate-decreasing effects of *l*-methadone, but not to the rate-decreasing effects of cocaine, and the degree of cross-tolerance was independent of FR size. These data suggest that behavioral cross-tolerance is modulated by pharmacological variables and not necessarily by reinforcement-schedule variables.

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