Pharmacology Biochemistry & Behavior, Vol. 32, pp. 347–354. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Oral Pentobarbital Intake in Rhesus Monkeys: Effects of Drug Concentration Under Conditions of Food Deprivation and Satiation

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Received 11 January 1988

KLINER, D. J. AND R. A. MEISCH. *Oral pentobarbital intake in rhesus monkeys: Effects of drug concentration under conditions of food deprivation and satiation.* PHARMACOL BIOCHEM BEHAV 32(1) 347–354, 1989.—Pentobarbital-reinforced behavior was studied in four rhesus monkeys. A pentobarbital solution and water were concurrently available during 3-hr sessions; water was freely available between sessions. Both pentobarbital concentration and feeding conditions (deprivation versus satiation) were varied. In two food-restricted monkeys subsequent food satiation eliminated pentobarbital-maintained responding. In two other food-restricted monkeys the effects of food satiation varied with the drug concentration. At the highest concentration, 4 mg/ml, food satiation did not alter responding, whereas at 2 mg/ml a moderate decrease occurred, and at 1 mg/ml responding was greatly reduced. During the food satiation phase, when the concentration was 4 mg/ml, responding was well maintained under several fixed-ratio sizes. Large quantities of pentobarbital were consumed, and intoxication was observed. Water-maintained responding occurred at low rates and did not vary across feeding conditions or drug concentration. The results support an interpretation in terms of a behavioral mechanism of action. Specifically, the effects of food deprivation on drug self-administration are to increase the magnitude of the reinforcing effects of the drug.

Food deprivation Food satiation Pentobarbital Drug reinforcement Drug self-administration
Oral route Drug concentration Fixed-ratio schedule Concurrent schedules Rhesus monkeys

PENTOBARBITAL is a sedative-hypnotic drug, specifically a barbiturate, that is often abused (22). Intravenously delivered pentobarbital functions as a reinforcer for baboons (18), rhesus monkeys (14, 17, 42, 45), and rats (12,15). Pentobarbital also serves as a reinforcer for rhesus monkeys when delivered orally (24–27, 33, 34) or intragastrically (1, 44, 46).

Early studies of drug reinforcement focused on variables such as drug type or class, drug dose, and reinforcement schedule. As the analysis of drug self-administration has progressed, additional variables have been studied (29), and one of these variables is food deprivation. Food deprivation often increases drug-reinforced behavior. Both intravenous (3, 5, 13, 38–40) and oral (6, 7, 24, 32, 36, 37) drug-reinforced performances are increased by food deprivation. When food deprived, rats drink more ethanol (36,37) and etonitazene (6, 7, 32), and rhesus monkeys drink more phencyclidine (8), pentobarbital (24), methohexital (11), d-amphetamine, and ketamine (10) than when food satiated. Also, when food deprived, rats intravenously self-administer more cocaine (5, 16, 39), amphetamine (16,40), etonitazene (3–5), phencyclidine (5), and heroin (38), and rhesus monkeys intravenously self-administer more cocaine (13) than when food satiated. Thus, increases in drug-reinforced behavior with food deprivation occur with different species, different classes of abused drugs, and with both the oral and intravenous routes.

In intravenous drug self-administration studies there is often an inverted U-shaped relation between dose and number of drug infusions (3,47). In oral drug self-administration studies there is also an inverted U-shaped relation between drug concentration and number of drug deliveries. Such a relationship is seen with both rats and rhesus monkeys (20, 31, 33) and with drugs such as ethanol (20,37), etonitazene (6,35), pentobarbital (33), and phencyclidine (8). The explanation for why drug deliveries eventually decrease as concentration is systematically increased is a matter of some dispute, but the decrease does not necessarily indicate decreasing reinforcing effects at higher concentrations. Results of studies employing several different designs point to the conclusion that over a range of doses or concentrations, higher drug amounts serve as better reinforcers than lower amounts (21, 23, 26–28, 34, 43).

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The finding that the relative reinforcing effects of higher drug concentrations are greater than those of lower concentrations can be used to further analyze how feeding conditions alter drug self-administration behavior. In the present study the pentobarbital-reinforced performance of rhesus monkeys was studied across a range of drug concentrations, first under conditions of food deprivation and then under conditions of food satiation.

GENERAL METHOD

Animals

Four adult male rhesus monkeys (*Macaca mulatta*) were housed in experimental chambers in a room illuminated 16 hr daily and maintained at 26.5°C. All four monkeys, M-BL, M-P, M-P1, and M-W, had experimental histories of oral ethanol (19,20) and pentobarbital (33) self-administration.

Apparatus

Stainless-steel primate cages (Labco No. ME-1305 or Hoeltge No. HB-108), having three solid walls and one barred wall, served as experimental chambers. Each cage was equipped with a response lever for food, two drinking devices for liquids, and corresponding stimulus lights mounted on one solid wall. The food lever was located centrally 40 cm above the cage floor. The drinking spouts were constructed entirely of brass and therefore electrically conductive at any point of contact. The two drinking spouts were located 30.3 cm apart horizontally on the same cage wall as the lever, and were 64 cm above the floor. Lip contacts on a drinking spout activated a solenoid for a maximum duration of 0.25 sec and delivered 0.6 ml of liquid. A break in contact during liquid delivery resulted in termination of solenoid operation, thus preventing spillage. Liquid and food availability were signalled by illumination of green (liquid) and red (food) stimulus lights, located 12 cm and 22 cm above the drinking spouts and food lever, respectively. Two pairs of feedback stimulus lights were located behind a Plexiglas plate which surrounded each drinking spout. One pair was covered with white lenses, and the other pair was covered with green lenses. The white and green lenses were correlated with the availability of water and drug, respectively. Each mouth contact with the spout illuminated the appropriate pair of lights (white or green) for the duration of the response. The temporal pattern of responses and deliveries was continuously recorded by cumulative recorders and by print-out counters that printed the data every ten minutes during sessions. Details of the apparatus and drinking device have been described elsewhere (19,30).

Food was delivered via a mechanical feeder (Ralph Gerbrands Co.) to a food hopper placed in the solid wall opposite the experimental panel. Solid-state programming equipment (Coulbourn Instruments, Inc.) located in an adjacent room was used for scheduling experimental events and recording responses.

Drug

Solutions of sodium pentobarbital were mixed in tap water approximately three hr prior to each session and presented at room temperature. Concentrations are expressed in terms of the salt.

Procedure

Daily experimental sessions were three hr in duration and were conducted seven days per week at a regular starting time. All sessions were preceded and followed by a 1-hr stimulus blackout period during which data were recorded and solutions were changed. During sessions steady illumination of the green stimulus light mounted 12 cm above a spout indicated water was available from that spout. Blinking of the green stimulus light above a spout indicated that pentobarbital was available from that spout.

During sessions water and a pentobarbital solution were concurrently available, one liquid from each spout. The spout at which pentobarbital was available alternated between the left and right sides from one session to the next. Since all monkeys had previously self-administered pentobarbital under various fixed-ratio (FR) schedules (24,25), high rates of pentobarbital-maintained responding were rapidly established. The FR values for each monkey were M-BL, FR 16; M-P, FR 18; M-P1, FR 64; and M-W, FR 64. In earlier studies with these monkeys there were reliable differences between pentobarbital and water maintained responding at these FR values (24). Each condition was studied until visual inspection of the data revealed no systematic trends in either the rate or pattern of responding over ten consecutive sessions.

During the 19-hr intersession period water was available under an FR 1 schedule from either the left or right spout. Water was delivered from the spout opposite the side of pentobarbital access in the upcoming daily session. Water access during both intersession periods and sessions was indicated by a steady illumination of the green stimulus light above the spout. Numbers of intersession lip-contact responses and milliliters of water consumed were recorded daily during the 1-hr blackout period prior to each session.

Access to food occurred only during the intersession period, and its availability was indicated by illumination of the red stimulus light mounted above the food lever. Food access began at the onset of the intersession period, following the 1-hr blackout period for recording data. The monkeys obtained their daily food allotment of Purina Monkey Chow (one cracker per delivery, weighing approximately 4.5 g) under FR schedules of lever presses. Food reinforcement schedules for each monkey were as follows: M-BL, FR 256; M-P, FR 128; M-P1, FR 64; and M-W, FR 64. Under food-satiation conditions, monkeys frequently obtain food but do not eat it, discarding it on the cage floor or outside the cage. The ratio values for each monkey were the lowest response requirement that minimized food obtained but not eaten. When food deprived, the monkeys typically responded steadily on the lever when the red light was on, and they always obtained their entire food allotment within the first hour of intersession food access. Body weights of the monkeys were determined every ten sessions and following completion of each experimental phase.

During sessions the monkeys were monitored via closed-circuit television. After a drinking bout, and at one and two hours into each session, each monkey's behavior was judged as falling into one of four categories: Rating 0, no observable effect; Rating 1, mild ataxia; Rating 2, severe ataxia; and Rating 3, anesthesia. This rating scale has been used previously in our laboratory (33).

EXPERIMENT 1: PENTOBARBITAL-REINFORCED PERFORMANCE AS A FUNCTION OF DRUG CONCENTRATION DURING FOOD DEPRIVATION

This experiment examined the effects of pentobarbital

TABLE 1
SEQUENCE OF CONDITIONS TESTED AND NUMBER OF 3-HR SESSIONS UNDER EACH CONDITION

PB conc. (mg/ml)	Food Condition	Minimum Number of Sessions Required	Number of 3-hr Sessions Required for Each Monkey			
			M-BL (FR 16)	M-P (FR 18)	M-P1 (FR 64)	M-W (FR 64)
4	Food Deprived	10	10	15	11	10
2	Food Deprived	10	17	17	12	15
1	Food Deprived	10	26	27	23	13
0.5	Food Deprived	10	23	13	12	10
0.25	Food Deprived	10	NT*	26	11	14
0.125	Food Deprived	10	NT	23	19	21
0.25	Food Deprived	2	NT	2	2	2
0.5	Food Deprived	2	NT	2	2	2
1	Food Deprived	2	2	2	2	2
2	Food Deprived	2	2	2	2	2
4	Food Deprived	10	23	26	14	17
4	Gradual Food Satiation	—	120	87	92	135

*NT=not tested.

concentration on pentobarbital-reinforced behavior during food deprivation.

METHOD

Procedure

The pentobarbital concentrations were presented in the following sequence: 4, 2, 1, 0.5, 0.25, and 0.125 mg/ml. Monkey M-BL was an exception in that the lowest concentration tested was 0.5 mg/ml. After this series of decreasing concentrations was completed, the monkeys were retested at 4 mg/ml. Prior to the 4-mg/ml retest, each of the intermediate concentrations was presented for two sessions in an ascending order. This was done to avoid problems that could follow an abrupt change from a very low to a very high concentration. At each concentration in the descending series and at the 4-mg/ml retest condition, ten sessions of stable performance were obtained. Water was concurrently available under an FR schedule of the same size as the schedule for pentobarbital. Table 1 lists the sequence of conditions and the number of sessions at each condition. The daily food allotments were 80, 70, 75, and 70 g for monkeys M-BL, M-P, M-P1, and M-W, respectively.

RESULTS AND DISCUSSION

Figure 1 shows that pentobarbital deliveries were an inverted U-shaped function of pentobarbital concentration. When the 4-mg/ml concentration was retested, the results were similar to the original 4-mg/ml values. The mean number of pentobarbital deliveries consistently exceeded the mean number of water deliveries. Water deliveries were low in number and did not vary systematically with the concentration of the concurrently available pentobarbital solution.

Figure 2 shows that for all monkeys the quantity of pentobarbital consumed (mg/kg/3-hr session) increased monotonically with increases in drug concentration. At some concentrations, drug intakes were sufficient to produce signs of intoxication that ranged from mild ataxia to anesthesia. In general, the severity of intoxication increased with increases in pentobarbital concentration (Table 2).

EXPERIMENT 2: PENTOBARBITAL-REINFORCED PERFORMANCE AS A FUNCTION OF AMOUNT OF FOOD AVAILABLE DURING THE 19-HR INTERSESSION PERIOD

This experiment examined the effects of gradual food satiation (2 g per day increases) on pentobarbital-maintained behavior.

METHOD

Animals and Apparatus

The same monkeys and apparatus were used as in the previous experiment.

Procedure

The monkeys were presented daily with concurrent access to 4 mg/ml pentobarbital and water. The FR values in the previous experiment were also used in this experiment. The food allotment during the 19-hr intersession period was increased at the rate of 2 g per day until each monkey failed to consume its entire food allotment for ten consecutive sessions. Table 1 lists the number of 3-hr sessions for each monkey during the gradual food satiation phase. To minimize uneaten food, the Purina Monkey Chow crackers were available under FR schedules. The FR values were: 256 for M-BL, 128 for M-P, and 64 for M-P1 and M-W. The FR size for M-W was later increased from FR 64 to FR 128 when the monkey began to obtain some food that it did not eat.

RESULTS AND DISCUSSION

Figure 3 shows the mean number of liquid deliveries across consecutive blocks of ten sessions in which the

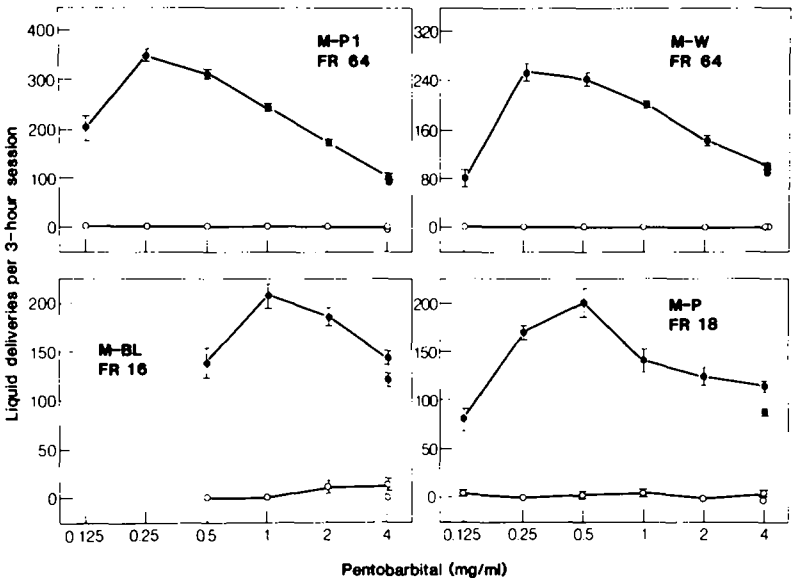

FIG. 1. Mean deliveries of pentobarbital (filled circles) and water (unfilled circles) per 3-hr session as a function of pentobarbital concentration (mg/ml) under conditions of food deprivation. Abscissa: pentobarbital concentration, log scale; ordinate: mean liquid deliveries. Each circle is a mean of the last ten sessions at each pentobarbital concentration. Brackets indicate the standard error of the mean except where the standard error is contained within the point. Unconnected circles represent retest values of 4 mg/ml pentobarbital and water. Note that the ordinate scale and the FR values differed among the monkeys.

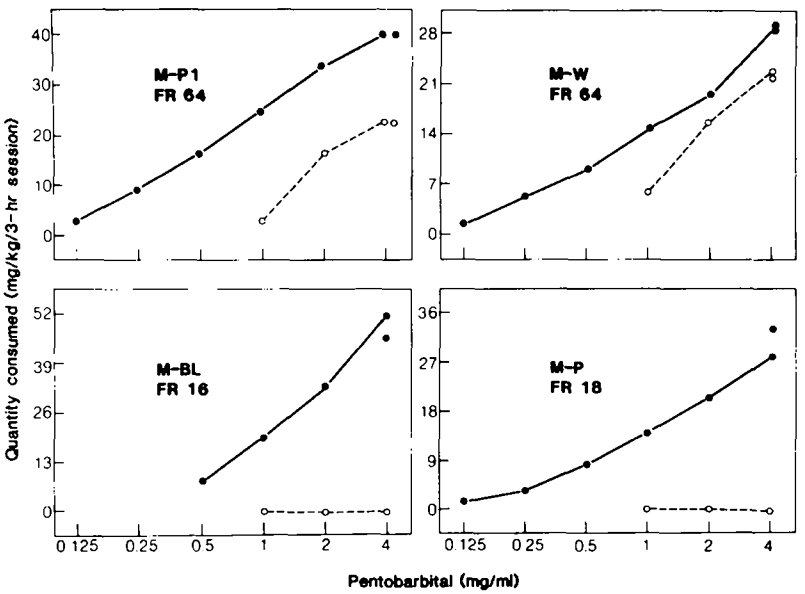

FIG. 2. Drug quantity consumed (mg/kg body weight/3-hr session) as a function of pentobarbital concentration (mg/ml) under conditions of food deprivation (filled circles with solid line) and satiation (open circles with dashed line). Abscissa: pentobarbital concentration, log scale; ordinate: quantity of pentobarbital consumed. The unconnected circles indicate retest values at 4 mg/ml pentobarbital and water. Each point is a mean of the last ten sessions at each pentobarbital concentration. Note that the ordinate scale and FR values differed among the monkeys.

TABLE 2

BEHAVIORAL RATINGS AS A FUNCTION OF PENTOBARBITAL CONCENTRATION UNDER FOOD DEPRIVATION CONDITIONS

		Behavioral Ratings						
		Pentobarbital Concentration (mg/ml)						
Monkey	FR Value	4.0	2.0	1.0	0.5	0.25	0.125	4.0 (retest)
M-BL	16	3	2.5	2	0	NT*	NT	3
M-P	18	1	1	1	0	0	0	1
M-P1	64	2.5	2	1.5	1	0	0	3
M-W	64	1	1	0	0	0	0	1

*NT=not tested.
Each rating is the peak effect observed at each pentobarbital concentration.

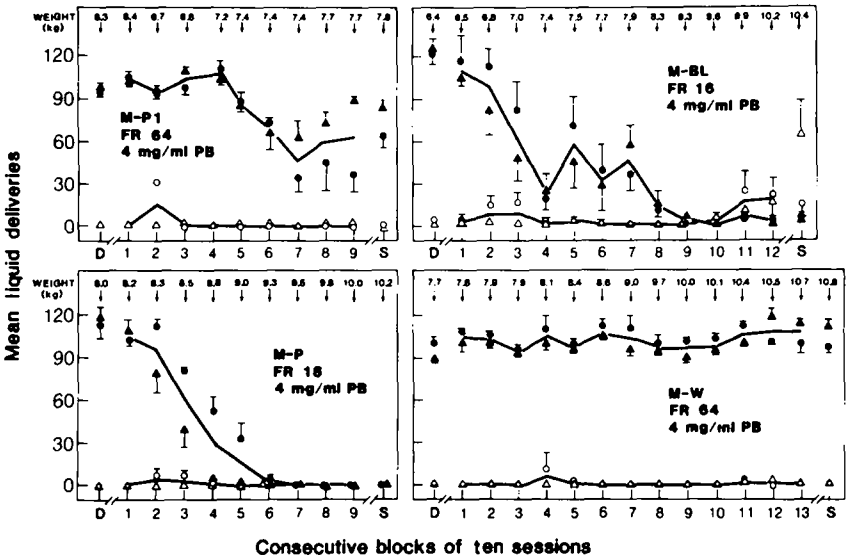

FIG. 3. Mean deliveries of 4 mg/ml pentobarbital (filled symbols) and water (open symbols) per 3-hr session during gradual food satiation (2 g of food per day). Abscissa: consecutive blocks of ten sessions; ordinate: mean liquid deliveries per 3-hr session. Each filled symbol is a mean of the pentobarbital values (n=10); each unfilled symbol is a mean of the water values (n=10). Circles represent the left side, and triangles represent the right side. Unconnected symbols above D and S indicate stable food conditions: food deprivation (D) or satiation (S). Numbers and arrows above the data points refer to the body weights of the monkeys (in kilograms). Note that the FR size differed among the monkeys.

amount of food available was increasing daily. In general, for all monkeys, water deliveries were infrequent. Gradual increases in the amount of food produced different changes in the number of 4-mg/ml pentobarbital deliveries for the four monkeys. For M-P1, the number of deliveries first decreased and later increased but remained less than initial values. For M-W, pentobarbital deliveries remained unchanged. With the final two monkeys, M-P and M-BL, the mean number of pentobarbital deliveries decreased to low levels. It is unclear why pentobarbital self-administration was not maintained in these two monkeys. However, the decrease in self-administration with increasing body weight cannot be attributed to a sudden change in interoceptive stimulus conditions since food satiation proceeded very gradually.

All four monkeys consistently gained weight in Experiment 2 (Fig. 3). When food satiated, the total food consumed per day by monkeys M-BL, M-P, M-P1, and M-W was 257.9, 267.8, 254.9 and 312.7 g, respectively.

EXPERIMENT 3: PENTOBARBITAL-REINFORCED PERFORMANCE AS A FUNCTION OF DRUG CONCENTRATION AND FR SIZE DURING FOOD SATIATION

In Experiment 2, two monkeys continued to self-

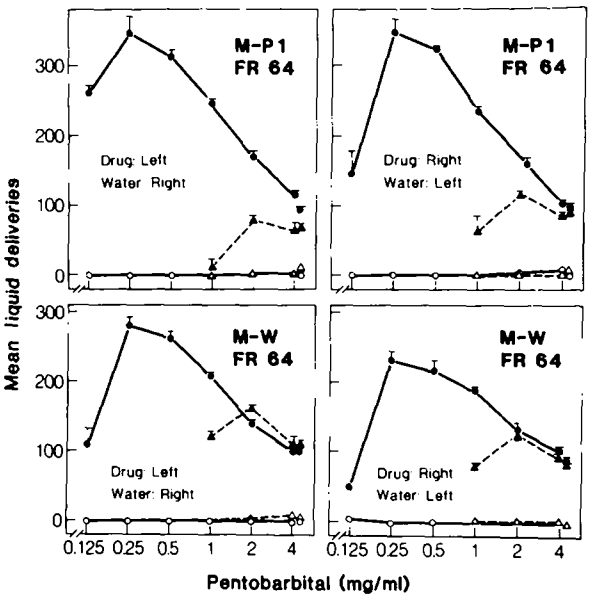

FIG. 4. Mean deliveries of concurrently available pentobarbital (filled symbols) and water (unfilled symbols) per 3-hr session as a function of pentobarbital concentration. Abscissa: pentobarbital concentration, log scale; ordinate: mean liquid deliveries. Food deprivation conditions are represented by circles, and food satiation conditions are represented by triangles. Each symbol is a mean of the last five sessions with pentobarbital and water concurrently available. Brackets indicate the standard error of the mean except where contained within the point. Unconnected symbols represent retest values of 4 mg/ml pentobarbital and water. Both the left and right sides were tested with drug and water concurrently available for each monkey. Note that the food deprivation values are from the first experiment and were illustrated in Fig. 1.

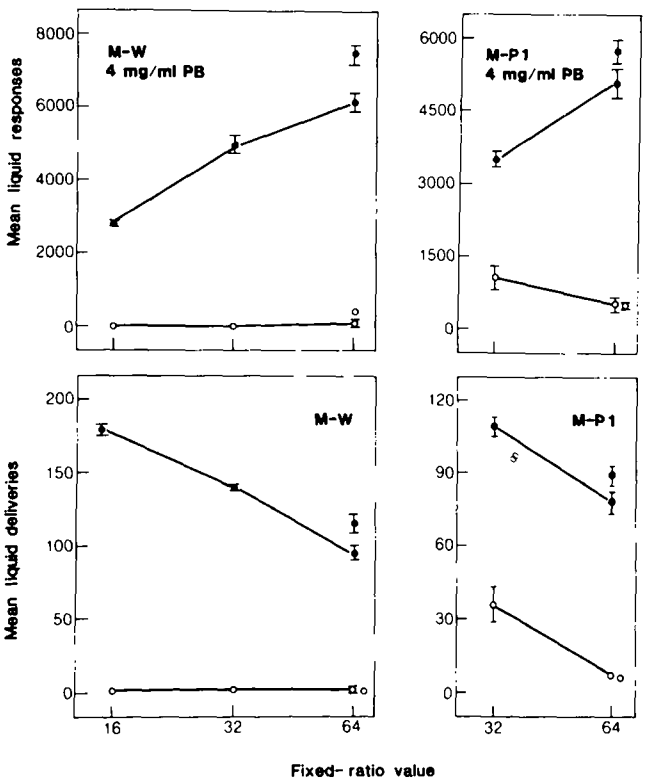

FIG. 5. Mean responses and liquid deliveries during food satiation as a function of FR size. Abscissa: FR value, log scale; ordinate: mean liquid responses (upper panels) or liquid deliveries (lower panels). Each circle is a mean of the last ten 3-hr sessions at each FR value. Filled circles represent drug values, and unfilled circles represent concurrent water values. The unconnected circles indicate retest values. Brackets indicate the standard error of the mean except where contained within the point. Note the ordinate scale differs for the upper and lower panels and between the two monkeys.

administer pentobarbital when food satiated. In the present experiment these two monkeys remained food satiated, and the effects of drug concentration and FR size were studied.

METHOD

Animals

Monkeys M-P1 and M-W were used in this experiment.

Apparatus

The apparatus was the same as in Experiments 1 and 2.

Procedure

With water concurrently available under an FR schedule of identical size, pentobarbital concentrations were presented in the sequence: 4, 2, 1, and 4 mg/ml (retest). Ten sessions of stable performance were obtained at each concentration. Between the 1-mg/ml concentration and the 4-mg/ml retest condition, the drug concentration was increased to 2 mg/ml for two sessions.

Subsequently, with pentobarbital concentration held constant at 4 mg/ml, a descending series of FR sizes was tested. The values tested were FR 64, 32, and 16 for M-W, and FR 64 and 32 for M-P1. After this series of FR values, both monkeys were retested at FR 64. Body weights were determined every ten sessions and following each change in FR size.

RESULTS AND DISCUSSION

Figure 4 shows that for M-P1 and M-W the mean number of pentobarbital deliveries was an inverted U-shaped function of drug concentration. The 4-mg/ml retest values were close to the original 4-mg/ml values. Thus, the decreases observed at 1 mg/ml were a function of the concentration and not due to a nonspecific decline in responding over the course of the experiment. When the values obtained during food satiation are expressed as a percentage of values during food deprivation, an orderly relationship is found: The greater the concentration, the greater was the number of drug deliveries when food satiated, as a percentage of the number when food deprived (85 and 91% at 4-mg/ml test and retest, respectively; 76% at 2 mg/ml; and 34% at 1 mg/ml). Deliveries of concurrently available water remained at low levels and were exceeded by deliveries of pentobarbital at all drug concentrations. The quantity of drug consumed (mg/kg body weight/3-hr session) increased with increases in the pentobarbital concentration, but at each concentration

pentobarbital intake was less than when the monkeys were food deprived in Experiment 1 (see Fig. 2).

Figure 5 shows that responding maintained by 4-mg/ml pentobarbital was directly related to FR size, but the number of drug deliveries was inversely related to FR size. Retest results at FR 64 were similar to initial values. Water-maintained performance was substantially less than drug-maintained performance. Monkeys M-P1 and M-W became severely ataxic at FR 32 and 16, respectively. Lower FR sizes were not tested to avoid risk of death from drug overdose. The persistence during the food satiation phase of both responding under FR schedules and intake of high amounts of pentobarbital demonstrates that for some monkeys pentobarbital can be an effective reinforcer even when food intake is not limited.

A pentobarbital concentration of 1 mg/ml did not maintain high rates of behavior under food satiated conditions. These results confirm earlier findings (24) and emphasize the importance of drug concentration as a determinant of drug-reinforced behavior.

GENERAL DISCUSSION

Thompson (41) has proposed that the notion of behavioral mechanisms of action provides a conceptual framework for organizing the behavioral effects of drugs. In essence, Thompson suggests that the behavioral effects of drugs should be analyzed in terms of changes in the effects of variables that normally control behavior, rather than postulating special mechanisms through which drugs' effects are manifested.

The findings of many studies of drug-reinforced behavior that have examined food deprivation as an independent variable can be integrated by a proposed behavioral mechanism of action, namely that food deprivation increases the reinforcing effects of drugs.

Evidence favoring such a mechanism consists of two types of findings. The first type of evidence is simply that many proposed alternative explanations have been ruled out. For example, studies in this area have repeatedly shown that the increases in drug-reinforced behavior under food deprivation conditions are not due to nonspecific increases in responding or to increases in intake of the drug vehicle [for a review see (9)]. The generality of the effect across routes, species, and pharmacological classes also eliminates many other possible explanations (9). The second type of evidence consists of specific findings. The largest increases in responding often occur with low or "threshold" doses (37,40). Increases occur even when interval reinforcement schedules are used, under which drug intake is not directly tied to response rate (2,13) and is limited regardless of response rate (2). Increases in response rate are also observed when access to drug is limited to a period at the end of the session (2). Such a procedure eliminates interactions between drug-maintained responding and drug actions other than its reinforcing effects (e.g., motor impairment).

A number of studies have shown that over a range of pentobarbital concentrations (from 4 mg/ml to 0 mg/ml), larger concentrations have greater reinforcing effects than lower concentrations. Two separate lines of evidence indicate greater relative reinforcing effects of higher concentrations: Higher concentrations are preferred to lower concentrations (34), and, relative to baseline, responding maintained by higher concentrations decreases less than responding maintained by lower concentrations, as FR size is increased (26). In the two monkeys whose responding persisted during gradual food satiation in Experiment 2, food satiation had no effect at 4 mg/ml, the most reinforcing concentration, and had the greatest effect at 1 mg/ml, the least reinforcing of the three concentrations tested. Thus, the present results provide further evidence for an increase in reinforcing effects due to food deprivation, but the results also suggest that the increase in reinforcing effects is not equal across drug concentrations. An important objective for future research is to determine if this differential effect across concentrations is real or only apparent. One would want to determine whether food deprivation produces increases in drug-reinforced responding at high concentrations when behavior is not limited by ceiling effects due to high intakes.

ACKNOWLEDGEMENTS

This work was supported by Grant DA 00944 from the National Institute on Drug Abuse. Dale J. Kliner was the recipient of National Research Service Award DA 05208 from the National Institute on Drug Abuse. This paper was based on the thesis submitted by Dale J. Kliner to the graduate school of the University of Minnesota in partial fulfillment of the requirements for the Ph.D. degree. Richard A. Meisch was the recipient of Research Scientist Development Award DA 00007 from the National Institute on Drug Abuse. We thank Drs. Marilyn Carroll, Carol Iglauer and Gregory Lemaire for their helpful comments on different drafts of this manuscript. The authors would also like to thank Gregory Lemaire, David Sauter, Ignatius Tan, Harley Rasmussen and Elizabeth Ungar for their technical assistance with this research project.

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