Pharmacology Biochemistry & Behavior, Vol. 16, pp. 579–584, 1982. Printed in the U.S.A.

The Effects of Food Deprivation and Satiation on Oral Pentobarbital Self-Administration in Rhesus Monkeys[1]

DALE J. KLINER[2] AND RICHARD A. MEISCH[3]

Psychiatry Research Unit, Box 392 Mayo, University of Minnesota, Minneapolis, MN 55455

Received 25 July 1981

KLINER, D. J. AND R. A. MEISCH. *The effects of food deprivation and satiation on oral pentobarbital self-administration in rhesus monkeys.* PHARMAC. BIOCHEM. BEHAV. 16(4) 579–584, 1982.—The effects of food deprivation and satiation on oral pentobarbital self-administration were studied in four rhesus monkeys. Pentobarbital (1.0 mg/ml) or water was available during alternate daily 3-hr session; between sessions, water was freely available. Lip contacts on a drinking spout activated a solenoid operated liquid delivery system. Liquid deliveries (0.56 ml) occurred after a fixed number of lip contact responses were emitted; that is, liquids were delivered according to fixed-ratio (FR) schedules. Under food deprivation conditions, pentobarbital-maintained behavior exceeded water-maintained behavior. Thus, pentobarbital functioned as a reinforcer. Abrupt unlimited access to food resulted in decreased pentobarbital intake. Pentobarbital-maintained behavior increased to previous levels when food intake was again restricted. In a second experiment, the effects of pentobarbital availability on water-maintained behavior were studied. Access to pentobarbital during alternate sessions produced elevated levels of water drinking during intervening sessions. Water drinking decreased to low levels when pentobarbital access was terminated and water was present for consecutive sessions. When pentobarbital was again available during alternate sessions, high levels of water drinking recurred. In the third experiment, water and pentobarbital (1.0 mg/ml) were concurrently available via separate drinking spouts. All three monkeys drank much more pentobarbital solution than water.

Food deprivation Food satiation Pentobarbital Self-administration Oral route Rhesus monkeys Response induction

FOOD deprivation produces increases in drug self-administration; this has been reported for a variety of psychoactive drugs such as cocaine [3,7], ethanol [17, 21, 22], etonitazene [2, 3, 4, 5, 19], phencyclidine [3,6], amphetamine [27], heroin [23], and nicotine [16]. These findings have been obtained in rats [2, 3, 4, 19, 21, 22] and rhesus monkeys [6,7], and occur when drugs are self-administered intravenously [2, 3, 7, 16, 23, 27] or orally [4, 19, 21, 22]. The findings that food deprivation produces increases in ethanol-maintained behavior [21,22] suggest that such increases may also occur with other sedative-hypnotic drugs.

The purpose of the present study was to examine the effects of food deprivation and satiation on oral pentobarbital self-administration in the rhesus monkey. Pentobarbital is a short acting barbiturate frequently abused by humans via the oral route [9,15]. Orally delivered pentobarbital can serve as a reinforcer for rhesus monkeys [8,20].

METHOD

Animals

Four adult male rhesus monkeys (*Macaca mulatta*) were individually housed in experimental chambers in a room illuminated 16 hr daily and maintained at 26.5°C. All four monkeys had served in studies of oral ethanol self-administration [11,13] and had recently served as subjects in an oral pentobarbital self-administration study [20]. Changes in body weight were made by varying the amount of Purina High Protein Monkey Chow (No. 5045) fed per day. The free feeding weights of monkeys M-BL, M-P, M-P1, and M-W were 8.6, 10.4, 8.1, and 10.2 kg, respectively. The monkeys were also given 1 ml of multiple vitamins (Vi-daylin, Ross Laboratories) once each week.

Apparatus

Experimental chambers were stainless steel primate

[1]This work was supported by Grant No. DA 00944 from the National Institute on Drug Abuse and by Grant No. AA 00299 from the National Institute on Alcohol Abuse and Alcoholism.

[2]This work was conducted in partial fulfillment of the requirements for Ph.D. thesis. Recipient of NIDA National Research Service Award DA 05208-01.

[3]Recipient of a Research Scientist Development Award DA 00007 from the National Institute on Drug Abuse.

cages (Labco No. ME-1305 or Hoeltge No. HB-108) having three solid walls and one barred wall. Each cage was equipped with a response lever for food, two drinking devices for liquids, and corresponding stimulus lights mounted on one solid side wall. A small brass contact plate (0.5 cm in dia.) was recessed one cm from the tip of each spout and was wired to a lip-sensitive drinkometer. The two drinking spouts were located 30.3 cm apart horizontally on the same cage wall. Lip contacts on a drinking spout activated a solenoid for a maximum duration of 0.25 sec and delivered 0.56 ml of liquid. A break in lip contact during liquid delivery resulted in termination of solenoid operation thus preventing spillage. Liquid and food availability were signaled by illumination of 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 a drinking spout. Responses for pentobarbital illuminated a pair of green lights, and responses for water illuminated a pair of white lights. A pair of lights remained on for the duration of each lip contact response. Details of the apparatus and drinking device have been described elsewhere [12,18]. Food was delivered via a mechanical feeder (Ralph Gerbrands Co.) to a food hopper 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 3 hr prior to each session and presented at room temperature. Concentrations are expressed in terms of the salt.

Procedure

Daily experimental sessions were 3 hr in duration and conducted seven days a week at a regular starting time. All sessions were preceded and followed by a 1-hr stimulus blackout for recording data and changing solutions. Water availability was signaled by steady illumination of a green stimulus light mounted 12.0 cm above the drinking spout. The green stimulus light blinked at a rate of 10 Hz when pentobarbital was available.

Presentation of a pentobarbital solution (1.0 mg/ml) or water was alternated daily during the first and second experiments. Since all monkeys had previously self-administered pentobarbital under various fixed-ratio (FR) schedules, high rates of oral pentobarbital self-administration were rapidly established and maintained with 1.0 mg/ml at various FR values [20]. The FR values for each monkey were: M-BL, FR 4; M-P, FR 16; M-P1, FR 45; and M-W, FR 32. These FR values resulted in the four monkeys obtaining similar numbers of pentobarbital deliveries. The sessions were conducted daily under these conditions until there was no trend in either pentobarbital or water deliveries for ten sessions. Behavior was judged stable when visual inspection of the data revealed no systematic trends in either rate or pattern of responding.

Food was given only during the intersession period and its availability was indicated by illumination of a red stimulus light mounted 22.0 cm above the food lever. Food access began at the onset of the intersession period exactly 1 hr after each daily session. The monkeys obtained their daily food allotment of monkey chow (one cracker per delivery weighing approximately 4.5 g) under fixed-ratio schedules of food reinforcement. A food delivery immediately followed completion of a fixed number of lever presses. Food schedules for each monkey were: M-BL, FR 256; M-P, FR 128; M-P1, FR 16; and M-W, FR 128. The ratio values used for each monkey were the lowest response requirements that minimized food waste. Food deprivation was imposed by limiting the daily food ration that could be obtained by each monkey. Under food deprivation conditions, all monkeys generally obtained their daily food allotments within the first hr of access.

Water was continuously available via a single drinking spout during the 19-hr intersession period under an FR 1 schedule. Water availability during intersession was indicated by a steady illumination of the green stimulus light used in daily sessions. Number of intersession lip contact responses and volume of water consumed were recorded daily during the 1-hr blackout period prior to each session.

Effects of food deprivation and satiation. Prior to the beginning of the first experiment, food deprivation was imposed by feeding 80 g, 70 g, 75 g, and 70 g of monkey chow to monkeys M-BL, M-P, M-P1, and M-W, respectively, to maintain each monkey between 70 to 75% of his free-feeding body weight. The body weights of the monkeys M-BL, M-P, M-P1, and M-W during the first food deprivation phase were 6.0 kg, 7.7 kg, 5.8 kg, and 7.1 kg, respectively. The food satiation phase consisted of unlimited access to food during the 19-hr intersession period for 30 days. This phase began immediately after completion of ten stable sessions of pentobarbital and water self-administration under food deprivation conditions. Finally, the food deprivation phase was reinstituted by restricting the daily food allotments to the previously determined amounts. Ten stable sessions were again obtained under the food deprivation conditions. The monkeys were weighed every ten days and also following completion of each phase.

Effects of pentobarbital access on water intake during 3-hr sessions. The same FR values (M-BL, FR 4; M-P, FR 16; M-P1, FR 45; and M-W, FR 32) and pentobarbital concentration (1.0 mg/ml) were used as in the first experiment. Pentobarbital or water was available during alternate sessions. A baseline of ten sessions (five sessions of access to pentobarbital and five sessions of access to water) was obtained for all four monkeys. This phase was followed by consecutive sessions of access to water that continued until the number of water deliveries was stable for five consecutive sessions. Finally, the monkeys were retested under the original conditions of alternating sessions of access to pentobarbital or water.

Daily food allotments consisted of 60 g, 53 g, 75 g, and 70 g of monkey chow for monkeys M-BL, M-P, M-P1, and M-W, respectively. Body weights were again monitored by weighing each monkey every ten days and following the completion of each experimental phase.

For monkeys M-P1 and M-W, the number of liquid deliveries for the final ten sessions of the food deprivation-satiation study was used as the baseline for this study. However, for monkeys M-BL and M-P the order of studies was reversed; the food deprivation-satiation manipulations immediately followed the study of pentobarbital access on water intake.

Concurrent access to 1.0 mg/ml pentobarbital and water. Three monkeys (M-BL, M-P1, and M-W) were trained to respond on the second drinking spout for 1.0 mg/ml pentobarbital. Access to pentobarbital was alternated daily be-

tween the left and right drinking spouts. Liquid deliveries were arranged according to an FR 32 schedule. Following ten consecutive sessions of stable performance maintained by pentobarbital (five sessions per side), concurrent access to water was added on the alternate spout. Liquid access on the two spouts was indicated by the green stimulus lights located 12.0 cm above each drinking spout. During each session, pentobarbital availability was signaled by blinking the green light above the appropriate spout while water availability was signaled by continuously illuminating the green light above the other spout. The stimulus lights located around each spout were also correlated with pentobarbital or water availability; that is, the green pair was illuminated for lip contacts on the pentobarbital spout and the white pair was illuminated for lip contacts on the water spout. During intersession, water access was alternated daily between the two spouts. The volume consumed was measured prior to and following each session. Pentobarbital was delivered from the spout that had not delivered water during the preceding 19-hr intersession period. All three monkeys were tested daily until ten consecutive sessions of stable pentobarbital and water-maintained performance were obtained.

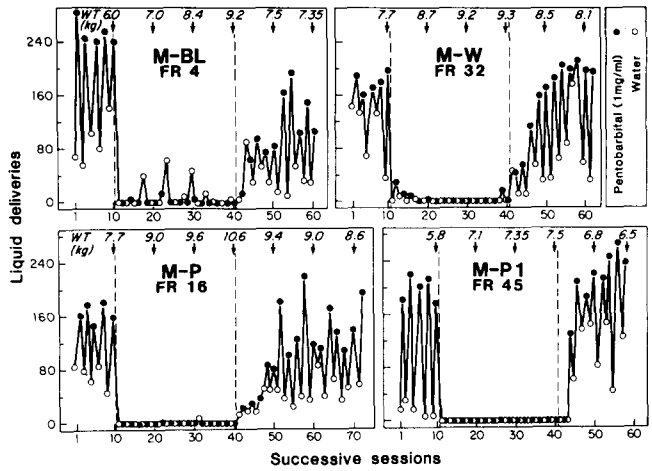

FIG. 1. Liquid deliveries of 1.0 mg/ml pentobarbital (filled points) or water (open points) are plotted as a function of food condition: deprivation (sessions 1–10), satiation (sessions 11–40), and re-deprivation (sessions≥41). Numbers and arrows above data points refer to the body weights of monkeys (in kilograms) and the respective days on which they were obtained. Note that the FR size differed for each of the four monkeys tested.

RESULTS

Effects of Food Deprivation and Satiation

Figure 1 shows that food satiation produced abrupt decreases in pentobarbital deliveries for all four monkeys. These decreases persisted throughout the entire 30 day food satiation phase (sessions 11–40). When the monkeys were again food deprived, pentobarbital deliveries gradually returned to former levels. During food deprivation (sessions 1 to 10 and 41 onward) rates of pentobarbital-maintained behavior remained consistently higher than rates obtained with water; however, water and pentobarbital maintained negligible rates of drinking during the food satiation phase.

Monkeys M-BL, M-P, M-P1 and M-W gained 3.2, 2.9, 1.7, and 3.5 kg, respectively during food satiation. The major proportion of total weight gained by the monkeys occurred during the first ten days of unlimited food access.

Reinstatement of food deprivation resulted in a gradual increase in pentobarbital and water-maintained behaviors (beginning after session 40). However, the rate of pentobarbital-maintained behavior generally exceeded the rate of water-maintained behavior during this phase (Fig. 1).

Intersession water drinking showed no systematic changes that corresponded with the changes in feeding conditions. During food satiation, intersession water consumption increased in one monkey (M-BL), decreased in two monkeys (M-P and M-W), and remained unchanged in one other monkey (M-P1). Table 1 summarizes the levels of intersession water consumption under conditions of food deprivation, satiation, and re-deprivation.

Table 2 lists the quantities of pentobarbital consumed under conditions of food deprivation, satiation and re-deprivation. Under food deprivation conditions, the monkeys consumed 11.8 (M-P) to 23.4 (M-BL) mg/kg body weight per session. Under food satiation conditions, the quantity of pentobarbital consumed decreased to zero. When conditions of food deprivation were reinstated, the pentobarbital intake ranged from 8.9 (M-P) to 22.6 (M-P1) mg/kg body weight per 3-hr session.

The pattern of pentobarbital-maintained behavior under food deprivation conditions showed characteristic FR per-

TABLE 1

MILLILITERS OF INTERSESSION WATER CONSUMED FOLLOWING DRUG AND WATER SESSIONS FOR CONDITIONS OF FOOD DEPRIVATION, SATIATION AND RE-DEPRIVATION

	Intersession Water Intake					
	Food Deprived		Food Satiated		Food Deprived (retest)	
Monkey	After Drug	After Water	After Drug	After Water	After Drug	After Water
BL	1684.0 (18.1)	1589.0 (24.8)	1951.6 (178.3)	2149.0 (109.6)	1414.0 (56.5)	1404.6 (37.8)
P	2100.0 (75.5)	2102.0 (45.0)	1206.2 (64.2)	1150.8 (21.1)	1850.0 (25.5)	1745.0 (50.3)
P1	1492.0 (43.3)	1527.2 (26.3)	1394.8 (125.2)	1422.8 (79.5)	1876.4 (22.9)	1799.0 (14.5)
W	1478.0 (114.2)	1630.0 (134.7)	882.0 (72.1)	1122.0 (212.9)	1301.0 (83.9)	1239.6 (124.3)
Group	1688.5 (62.8)	1712.1 (57.7)	1358.7 (110.0)	1461.2 (105.8)	1610.4 (47.2)	1547.1 (56.7)

Values are means of last five 19-hr intersession volumes and standard errors. Group values are means of four monkeys tested and mean standard errors.

TABLE 2

QUANITY OF PENTOBARBITAL CONSUMED (mg/kg BODY WEIGHT/3-hr SESSION) DURING CONDITIONS OF FOOD DEPRIVATION, SATIATION, AND RE-DEPRIVATION

Monkeys	Liquid Schedule	Food Deprived	Food Satiated	Food Deprived (retest)
M-BL	FR 4	23.4	0	10.5
M-P	FR 16	11.8	0	8.9
M-P1	FR 45	19.3	0	22.6
M-W	FR 32	12.5	0	13.2

Values are means of last five drug sessions under each condition.

formance. All four monkeys responded at high steady rates until a ratio was completed. Following a drug delivery, there was a pause in responding prior to the initiation of the next ratio. Generally, pentobarbital deliveries occurred in bursts throughout the session, whereas water deliveries were dispersed over the entire session. The overall pattern of pentobarbital deliveries was negatively accelerated.

Effects of Pentobarbital Access on Water Intake During the 3-hr Sessions

Figure 2 shows that in the absence of access to pentobarbital during alternate sessions, water-maintained behavior decreased and remained at low levels. When pentobarbital access was reinstated during alternate sessions, increases in pentobarbital-maintained behavior were followed by increases in water-maintained behavior. Thus, maintenance of elevated water intake within intervening sessions was due to pentobarbital access during alternate sessions. For one monkey, M-P1, responding maintained by water continued to increase until it was within the range of responding maintained by pentobarbital. The fixed-ratio value was then increased from FR 45 to FR 64 at which point water intake was substantially lower than pentobarbital intake.

Intersession water drinking showed no systematic changes across experimental conditions although the intersession water drinking did become more variable when water was present during consecutive sessions. The monkeys did not vary in body weight by more than 0.4 kg and continued to consume their entire food allotments within the first hr of access.

Concurrent Access to 1.0 mg/ml Pentobarbital and Water

Figure 3 shows that mean pentobarbital deliveries always exceeded mean water deliveries. This was true regardless of the side positions of water and pentobarbital. Mean liquid deliveries of pentobarbital ranged from 205.3 (M-BL) to 417.3 (M-P1). The monkeys M-BL, M-P1, and M-W consumed 18.6, 33.5, and 17.7 mg/kg body weight of pentobarbital, respectively. The pattern of pentobarbital and water-maintained responding showed characteristic FR performance consistent with response patterns observed in the first experiment.

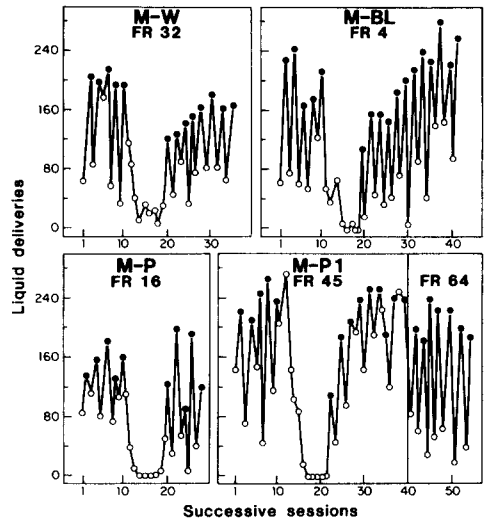

FIG. 2. Liquid deliveries of 1.0 mg/ml pentobarbital (filled points) or water (open points) are plotted for consecutive 3-hr sessions. Sessions 1–10 show liquid deliveries of pentobarbital and water. Pentobarbital access was terminated after session 10, and only water was available for each consecutive session. Pentobarbital access was reintroduced in sessions, 19, 18, 23, 20 for monkeys M-BL, M-P, M-P1, and M-W, respectively. Note that the FR value for M-P1 was increased from FR 45 to FR64 at session 40 and that the FR size differed for each of the four monkeys tested.

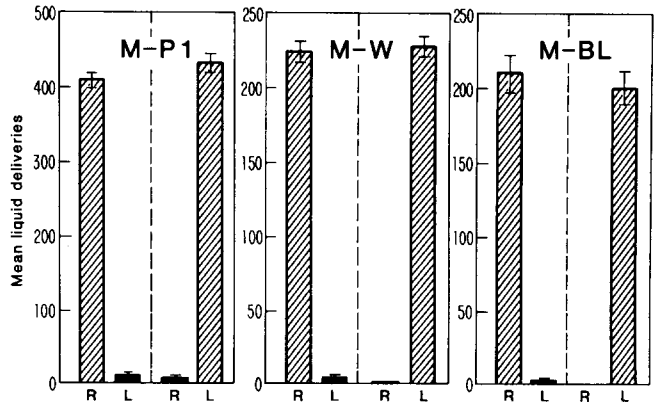

FIG. 3. Mean pentobarbital and water deliveries per 3-hr session under conditions for concurrent access. Ordinate: mean liquid deliveries; Abscissa: left (L) or right (R) sides tested. Each bar is a mean of the last five sessions and filled bars represent water sessions. Brackets indicate S.E.M. All three monkeys were tested at FR 32.

DISCUSSION

These findings demonstrate that food deprivation increases and food satiation decreases oral pentobarbital self-administration behavior in rhesus monkeys. Food satiation produced marked decreases in pentobarbital-reinforced behavior which remained at low levels throughout the entire 30 day food satiation phase. It is interesting that these decreases occurred after only a single 19-hr intersession period of unlimited access to food. Thus, the drop in rates of pentobarbital self-administration occurred even though body

weights were close to their food deprivation levels. A return to food deprivation produced a gradual recovery of pentobarbital-maintained behavior to levels obtained under the prior food deprivation phase. The recovery of pentobarital-reinforced behavior occurred at higher body weights than their previous food deprivation weights. Within 12 sessions after the onset of the second food deprivation phase, the rates of pentobarbital-maintained behavior were within the range of previous food deprivation values although body weights were between 81.5% to 91.4% of their food satiated values. Similar findings have been noted with rhesus monkeys in a study of oral phencyclidine self-administration [6]. These findings indicate that changes in the quantity of available food are important determinants in altering drug-reinforced behavior.

There is evidence that the changes in pentobarbital-reinforced behavior during the different food conditions were not secondary to changes in water intake. First, during the food deprivation phases, intake of pentobarbital solutions consistently exceeded intake of water which served as the vehicle. Second, water intake during the 19-hr intersession periods showed no systematic changes across food conditions. Third, in the food deprivation phases, the elevated water drinking during intervening sessions was due to the presence of pentobarbital during alternate sessions. Finally, Carroll and Meisch [6] reported no changes in water intake across food conditions in monkeys orally self-administering phencyclidine. Therefore, the increases in pentobarbital-maintained behavior produced by food deprivation were not secondary to increases in water intake.

Earlier research has shown that food deprivation increases ethanol intake of rats (for a review see [17]). These increases have been attributed to the caloric value of ethanol [10]. The present results show that food deprivation increases oral self-administration of another sedative-hypnotic drug, namely pentobarbital. The absence of calories in pentobarbital rules out a caloric interpretation. Thus, the findings of the present study in addition to other studies [1, 14, 17, 21, 22, 26] suggest that increased intake of ethanol during food deprivation cannot be attributed solely to its caloric value.

Access to pentobarbital during alternate sessions elevated water intake during intervening sessions when the monkeys were tested using a single drinking spout. Several interpretations of pentobarbital's role in elevating water drinking can be ruled out based on the findings of the present study. It is unlikely that the elevated levels of water drinking were due to a pharmacological interaction of pentobarbital with water drinking since intersession water intake following pentobarbital access did not differ from intersession water intake following water access. Furthermore, the results of concurrent access to pentobarbital and water demonstrate that the monkeys were able to discriminate between the two solutions. One possible interpretation is that the elevated water-maintained responding is due to response induction. Positive response induction occurs when an increase in response rate in one component is a function of an increase in response rate in another component [24,25]. In the present study, elevated rates of water-maintained responding occurred only when there were high rates of pentobarbital-maintained responding during alternate sessions.

This study confirms earlier reports [8,20] that pentobarbital may function as an orally effective reinforcer for rhesus monkeys. Specifically, the rate of pentobarbital-maintained behavior exceeded the rate of water-maintained behavior when pentobarbital and water were presented sequentially or concurrently. Also, the pattern of pentobarbital-reinforced behavior under FR schedules was similar to the pattern of FR responding observed with other reinforcers.

Food deprivation and satiation produced changes in pentobarbital-maintained behavior similar to the changes observed with drugs from other pharmacological classes. The findings of the present study are consistent with earlier research with cocaine [3], ethanol [17, 21, 22], etonitazene [2, 3, 4, 5, 19], amphetamine [27], heroin [23], and nicotine [16] self-administration in rats as well as with oral phencyclidine [6] and intravenous cocaine [7] self-administration in rhesus monkeys. These studies show that food deprivation is a potent variable that increases drug self-administration by animals, and that the effects of food deprivation are consistent across several drug classes and routes of administration. The present study extends the generality of these earlier findings to include pentobarbital.

ACKNOWLEDGEMENTS

The authors would like to thank Patrick Beardsley, Gregory Lemaire, and Dace Svikis for their technical assistance and Philip Catchings, Drs. Marilyn E. Carroll, James P. Goldberg, Jack E. Henningfield, and Sandra Schrader for their helpful comments on the manuscript.

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