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Food Deprivation Alters Behavioral and Plasma Corticosterone Responses to Phencyclidine in Rats[1]

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COVENEY, J. R., B. S. NEAL AND S. B. SPARBER. *Food deprivation alters behavioral and plasma corticosterone responses to phencyclidine in rats.* PHARMACOL BIOCHEM BEHAV **36**(3) 451–456, 1990.—Phencyclidine (PCP) sensitivity of rats, whose body weights were maintained at 70% of free-feeding controls, was compared to drug sensitivity of the controls in terms of unconditioned (exploratory) behavior and plasma corticosterone levels. Low doses of PCP HCl [0 (saline vehicle), 0.3 or 0.9 mg/kg, SC] were given to food-deprived rats and to free-feeding controls 15 minutes before measuring unconditioned behavior for 90 minutes; then PCP in brain and corticosterone in plasma were assayed. An additional group (0.43 mg/kg) was established from the reduced-weight rats in order to compare with free-feeding rats given 0.3 mg/kg, the same absolute dose—a circumstance reflecting "street" usage in which doses are not adjusted for body weight differences among users. These low doses of PCP altered exploratory behaviors, but there did not appear to be an interaction between food-deprivational status and drug, with the possible exception of an altered effect of PCP upon habituation in the lighter animals. PCP elevated plasma corticosterone levels over saline controls only in the reduced-weight rats. The drug, possibly reflecting a tranquilizing action of the lowest dose, reduced corticosterone levels in free-feeding controls. Brain levels of drug were directly related to dose, and were elevated in the food-deprived animals 26–30% over those at the same per-weight dose levels in the free-feeding rats, in spite of being given lower absolute amounts of drug. In the 0.43 mg/kg reduced-weight dose group, given the same absolute dose as the 0.3 mg/kg free-feeding group, brain levels were doubled over the latter group, and exploratory behavior was correspondingly different from the free-feeding group. Behavioral and endocrinological consequences of lipophilic drugs (like PCP) are magnified in states of weight loss with fixed-amount dose regimens, and this might have a dispositional basis.

Phencyclidine Food deprivation Unconditioned behavior Corticosterone Stress

REDUCTION of body weight by restricted access to sources of nutrition has been shown to alter a variety of responses to psychoactive and autonomic drugs: Kast and Nishikawa (5) found that overnight food deprivation enhanced the lethal actions of orally administered cholinergic antagonists and β-adrenergic agonists and antagonists. They attributed this effect to increased absorption from the gastrointestinal tract because they observed no increase in lethality resulting from food deprivation when one of the compounds was injected by the intraperitoneal route. On the other hand, Masur and Ribeiro (7) found chronic undernutrition to reduce the sleep time of ethanol- or pentobarbital-treated rats, while twenty-four-hour food deprivation enhanced sleep time. Campbell and Fibiger (2) found a strong interaction between another psychomotor stimulant, dextroamphetamine, and acute food deprivation. Food deprivation augmented dextroamphetamine's increase in spontaneous motor activity of rats. An enhanced locomotor response to the drug was seen after as little as one day of food deprivation. These authors ascribed this interaction to the neurochemical, electrophysiological and behavioral "arousal" of starvation acting synergistically with that of dextroamphetamine.

Body weight reduction of rats has been shown to enhance a behavioral action of moderate to high doses of phencyclidine (PCP), as well. Woolverton, Martin and Balster (15) described an enhanced ability of PCP, at 4 to 8 mg/kg, to reduce milk consumption by rats reduced in weight to 71% of a free-feeding group. Evidence for a dispositional cause of this effect was provided by the authors, in that higher brain levels of the drug were found in the lower-weight group 30 minutes after an acute injection.

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Smaller doses of PCP may more closely reflect that which may be liberated by stress from tissue stores of PCP after discontinuing chronic use. No evidence has appeared which supports the notion that behavioral or other actions of small doses of PCP will be enhanced by food deprivation stress or alterations in PCP distribution due to a loss of adipose storage sites. This study was undertaken to examine the actions and disposition of small doses in animals subjected to weight reduction by chronic food deprivation.

Part of the "arousal" response to food deprivation includes hypophyseal-adrenocortical activation, an effect which is also incurred as a response to many drugs. Fahringer, Foley and Redgate (4) and Nisticò *et al.* (10) have shown that moderate to anesthetic doses of ketamine, a short-acting anesthetic chemically and pharmacologically classed with PCP, will elevate plasma corticosterone levels in rats. Pechnick *et al.* (11) reported that PCP, at doses of 1 or 10 mg/kg, also increases plasma corticosterone levels in rats. Plasma corticosterone levels remained above controls for at least two hours after the high dose, but levels had returned to control values after the low dose by that time. Because no data have appeared in the literature concerning the actions of PCP, at low doses, upon adrenocortical response, and because of the importance of this endocrine system in the stress response, plasma corticosterone levels were included as a measure of the response to food deprivation and low doses of PCP in rats.

METHOD

Male Long-Evans rats (323–387 g, initially) from Blue-Spruce Farms (Altamont, NY) were housed individually in hanging wire mesh cages ($20 \times 25 \times 18$ cm) in a temperature-controlled (22 ± 1°C) and humidity-controlled (40–50%) environment under a 12-hour light/dark cycle (on from 0700 hr). The heaviest rats were placed on restricted rations of their standard laboratory rat diet (Purina Rat Chow) to gradually reduce their weights to 275–323 g. Once this weight range was attained, it was maintained until the test days by adjusting daily food rations. Remaining rats were kept with food available ad lib until test days.

To minimize diurnal variations in results, only one rat from each group was tested on any experimental day, so that testing could be done at approximately the same time each day (at about 1400 hr; 22–26 hr after the last food ration for the food-deprived rats). On the test day, rats were transferred from the animal quarters to a holding room adjacent to the behavioral testing room and allowed at least one hour to acclimate. On each test day, four food-deprived rats were randomly allocated among four treatment groups to receive saline vehicle (1 ml/kg) or tritium-labelled PCP hydrochloride (approximately 5 μCi/kg; National Institute on Drug Abuse, Rockville, MD) at 0.3, 0.43 or 0.9 mg/kg. Three other rats were taken from the pool of free-feeding rats and assigned, on the basis of body weight, to receive vehicle, 0.3 or 0.9 mg tritium-labelled PCP HCl/kg. On each test day, free-feeding rats (393–460 g) were matched to those in the food-deprived cohort such that the latters' body weights were about 70% (67–71% on an individual basis) of the formers'.

The 0.43 mg/kg dose was included in the deprived group because it represented the same absolute dose (mg per rat) given to the free-feeding rats assigned to receive 0.3 mg/kg. Since the clinical relevance of these studies was of importance, we reasoned that PCP users would not ordinarily adjust their doses based upon body mass or fat content. Therefore, one of the important statistical contrasts were between the deprived group given 0.43 mg/kg and the fed group given 0.3 mg/kg.

Injections were made subcutaneously in the flank 15 minutes before the beginning of 90-minute behavioral sessions in standard small animal operant chambers designed to measure unconditioned (exploratory) behaviors. Solid-state touch circuits were used to detect contact with an operant lever and with a 7.5 cm wide stainless steel wall strip attached to two walls 15 cm above the stainless steel grid floor of the operant chambers. Contacts with either lever or wall strip, which had no programmed consequences, completed an electrical circuit to the grid floor with an impedance of less than 2.5 megohms. Wall strip contacts were used as an index of rearing (12,13), and lever contacts served as an additional simultaneous measure of horizontal exploratory behavior. Sessions were controlled by commercial microprocessors (TRS-80 Color Computers, Tandy Corporation, Dallas, TX) by means of custom made interface equipment. Data were recorded on magnetic tapes at the end of each session for later hardcopy printing.

When its session had ended, each rat was removed from the operant chamber and decapitated. Brains were removed and stored at −70°C until assayed for PCP by the method of Misra, Pontami and Bartolomeo (9). Trunk blood was collected in beakers containing 0.1 ml sodium heparin (1000 U/ml) and was centrifuged at $250 \times g$ for 20 minutes at 4°C. Plasma was recovered and stored at −70°C until assayed for corticosterone by modifications of the method of Alvinerie and Toutain (1), and Matsuzawa, Shugimoto and Ishiguro (8): 0.1 ml plasma samples, combined with 100 ng prednisolone (in 0.1 methylene chloride) as an internal standard, were made alkaline with 0.01 ml 1.25 N NaOH and extracted with 1.5 ml methylene chloride by vortexing for about 30 seconds. Extraction tubes were centrifuged at $250 \times g$ for 4 minutes at 4°C. A 1.4 ml aliquot of each organic phase was dried under a stream of nitrogen and then reconstituted in 0.2 ml methylene chloride. An 0.1 ml aliquot of this solution was chromatographed on an adsorption column (μPorasil, Waters Associates, Milford, MA) in a high performance liquid chromatography system (Model 420 controller and 110A pump, both Beckman, Fullerton, CA). All reagents were HPLC grade (J. T. Baker Chemical Co., Phillipsburg, NJ). Steroids were eluted at 2 ml/min with methylene chloride:methanol:acetic acid (97:3:0.3) and steroids were quantified in the eluate by monitoring absorbance at 254 nm (LDC Duo Monitor, Milton Roy, Riviera Beach, FL). Spectrophotometric output was low-pass filtered at 0.01 Hz (Spectrum Model 1021A, Spectrum Science Co., Newark, DE) and recorded (integrator Model 3390A, Hewlett Packard, Chicago, IL). Retention times for corticosterone and prednisolone (both from Sigma Chemical Co., St. Louis, MO) were 3.5 and 6.5 minutes, respectively.

Data were subjected to analysis of variance and Student's *t*-statistic or Duncan's New Multiple Range test. Behavioral data were summed in blocks of 30 minutes and square root-transformed before analyses. Transformation of the behavioral data (existing in the form of counts) was indicated as a variance-stabilizing step [(14), p. 399].

RESULTS

Lever contacts (Table 1A) made by rats given PCP differed from those made by rats in the control group, $F(3,35) = 6.75$, $p < 0.05$, but there was no overall effect of food deprivation, $F(1,35) = 2.00$, nor was there an interaction between drug treatment and food deprivation, $F(2,35) = 1.87$. When collapsed across the food-deprivation factor, lever contacting at the 0.43 mg/kg and 0.9 mg/kg dose levels was significantly greater than at the saline level, but there was no statistically significant difference between doses. Figure 1 shows the decline in this exploratory behavior as time progresses. $F(2,70) = 78.25$, $p < 0.05$, reflecting adaptation to the novel environment. Also shown is retarded adaptation in

TABLE 1

UNCONDITIONED BEHAVIORS IN FREE-FEEDING AND FOOD-DEPRIVED RATS AFTER PHENCYCLIDINE

A. Lever Contacts (square root-transformed)/30-Minute Block

	Dose of Phencyclidine HCl (mg/kg)			
	0	0.3	0.43	0.9
Free-feeding	3.80 ± 0.47 (6)	4.51 ± 0.47 (6)	—	7.27 ± 0.66 (7)*
Food-deprived	4.98 ± 0.68 (5)	6.16 ± 0.25 (6)	7.29 ± 0.83 (6)*	6.66 ± 0.83 (6)*

B. Wall-Strip (square root-transformed) Contacts/30-Minute Block

	Dose of Phencyclidine HCl (mg/kg)			
	0	0.3	0.43	0.9
Free-feeding	4.54 ± 0.45 (6)	7.20 ± 2.17 (6)	—	7.70 ± 0.60 (7)
Food-deprived	5.49 ± 0.56 (5)	6.74 ± 0.93 (6)	7.96 ± 0.94 (6)	6.90 ± 0.34 (6)

Square root-transformed contacts in each 30-minute block were averaged across the 90-minute session for each animal. Values reported represent group means of these averages ± SE. The number of animals per group is indicated in parentheses.

*Statistically significantly different from saline group (main effects for food deprivation), Duncan's New Multiple Range test, $p<0.05$.

phencyclidine-treated animals, reflected in a dose by time-block interaction, $F(6,70)=8.38$, $p<0.05$. Although there was no deprivational state-related main effect upon adaptation, $F(2,70)=0.00$, the basis of a three-way interaction term, $F(4,70)=2.43$, $p=0.056$, remains obscure.

There was a trend in drug-produced alterations in strip contacting (rearing) (Table 1B), $F(3,35)=1.79$, $p=0.088$, but again, no differences due to food deprivation, $F(1,35)=0.02$, or its interaction with drug, $F(2,35)=0.38$, was evident. Adaptation was also reflected in declining rates of rearing as time progressed (Fig. 2), $F(2,70)=47.19$, $p<0.05$. Again, the decline of rearing exploratory activity was interrupted by PCP, $F(6,70)=9.29$, $p<0.05$.

Brain levels of PCP (Table 2) were directly related to dose, as expected, $F(2,27)=71.56$, $p<0.05$. More important was the finding that food deprivation elevated the levels of drug in the brain 105 minutes after administration, $F(1,27)=8.29$, $p<0.05$. Food-deprived animals receiving 0.3 mg PCP/kg had 26% higher brain PCP levels compared to the free-feeding group at that dose, and those at the 0.9 mg/kg level had 30% higher levels compared to their free-feeding comparison group. It must be remembered

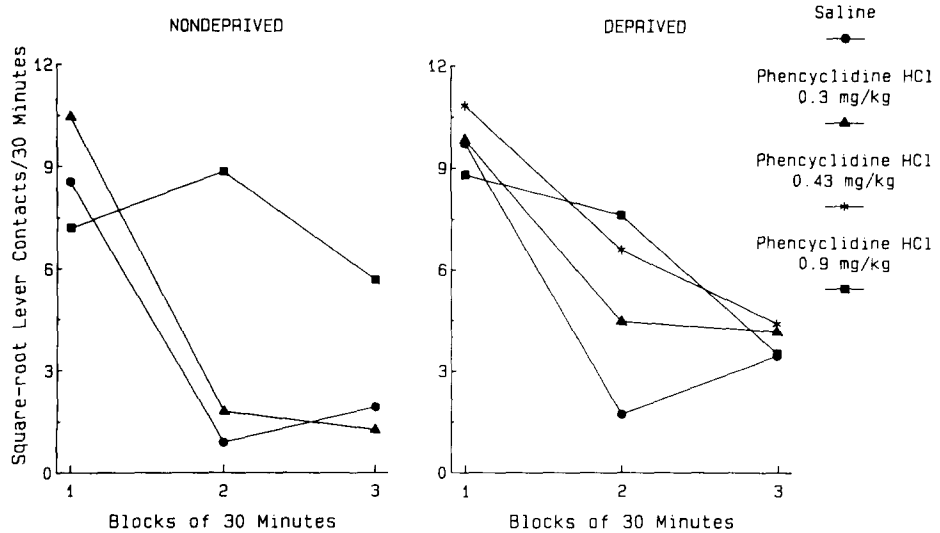

FIG. 1. Phencyclidine actions upon lever contacting in free-feeding and food-deprived rats. Lever contacts made by free-feeding (left panel) and food-deprived (right panel) rats during a 90-minute unconditioned behavior session were summed in three consecutive 30-minute blocks before square root-transformation and averaging.

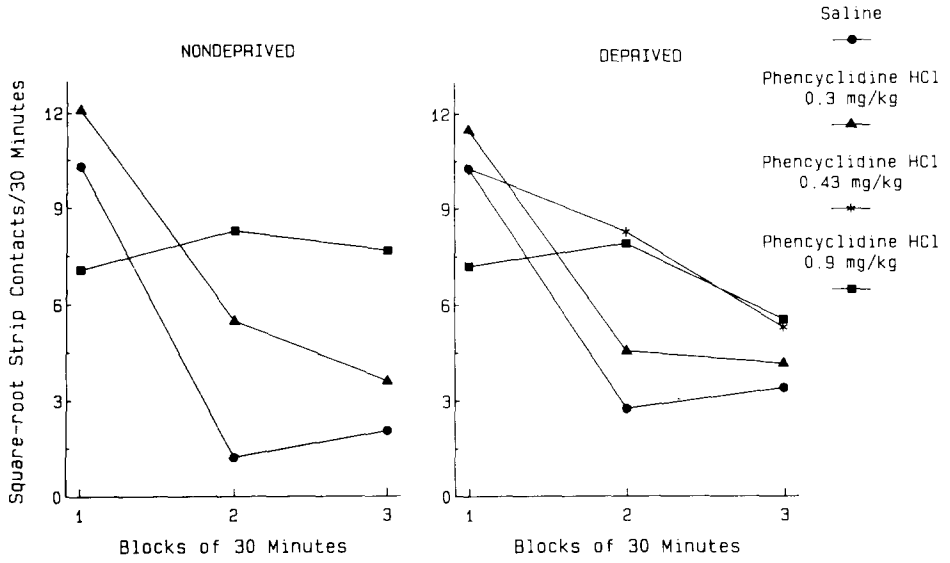

FIG. 2. Phencyclidine actions upon wall-strip contacting (rearing) in free-feeding and food-deprived rats. Wall-strip contacts made by free-feeding (left panel) and food-deprived (right panel) rats during a 90-minute unconditioned behavior session were summed in three consecutive 30-minute blocks before square root-transformation and averaging.

that this is a conservative comparison, since the weight differences meant the deprived groups received considerably less drug than the fed groups.

Of further interest, from a clinical perspective, food-deprived rats given the same absolute dose (mg/rat) as the free-fed group given 0.3 mg/kg (i.e., the 0.43 mg PCP/kg group) showed a doubling of brain PCP levels 105 minutes after injection: 68.8 vs. 37.1 ng/g, $t(10)=4.83$, $p<0.05$. This was also reflected by increased lever contacting: 7.29 vs. 4.51 square-root transformed contacts per 30 minutes, $t(10)=2.91$, $p<0.05$.

Changes in plasma corticosterone levels (Table 3) due to food-deprivational state, $F(1,36)=11.59$, $p<0.05$, and PCP dose, $F(3,36)=2.78$, $p=0.055$, were apparent. An interaction, $F(2,36)=2.50$, $p=0.097$, was also suggested by the data. The food-deprived saline control group seemed to have accommodated to the stress of deprivation. Their plasma corticosterone levels were no different from the free-feeding group's. However, the food-deprived groups responded to PCP quite differently from nondeprived groups, in correspondence with elevated brain levels of PCP: 0.3 mg/kg resulted in higher corticosterone levels, $F(1,10)=8.28$, $p<0.05$, than those of the free-feeding group at that dose level. The same absolute dose (0.43 mg/kg) given to the deprived animals also resulted in corticosterone levels higher than those in the 0.3 mg/kg free-feeding group, $t(10)=4.40$, $p<0.05$, the latter demonstrating a fall in plasma corticosterone levels compared to the free-feeding saline control group, $t(10)=3.11$, $p<0.05$.

TABLE 2

DRUG LEVELS IN BRAINS OF FREE-FEEDING AND FOOD-DEPRIVED RATS AFTER PHENCYCLIDINE

	Dose of Phencyclidine Hydrochloride (mg/kg)		
	0.3	0.43	0.9
Free-feeding	37.0 ± 3.7	—	112.5 ± 10.5*
Food-deprived	46.7 ± 2.4	68.8 ± 6.2†	146.7 ± 11.5*

Values indicate average concentration of phencyclidine base (ng/g brain) ± SE at 105 minutes after SC administration for n = 6, except at the 0.9 mg/kg dose, where n = 7.

*Significantly different from 0.3 mg/kg dose level, $p<0.05$; Duncan's New Multiple Range.

†Significantly different from free-feeding low-dose group, $p<0.05$; Student's t-statistic.

DISCUSSION

Woolverton, Martin and Balster (15) demonstrated that higher brain levels of PCP in food-deprived rats were associated with a greater reduction in milk consumption after a high dose (4 mg/kg) of the drug was given intraperitoneally. In their study, concentrations of PCP found in some tissues of food-deprived rats were higher than in free-feeding rats; the reverse was true of intestinal PCP content 30 minutes after injection, suggesting one mechanism by which other tissues may have been elevated: *via* a more rapid rate of absorption from the intraperitoneal site of administration in food-deprived rats compared to the rate of absorption from this site in free-feeding rats.

As time passes and the absorption phase is more nearly complete, the relative contribution of a drug's absorption rate upon its tissue levels declines. To the extent that the influence of an altered absorption rate is diminished as time passes after injection, the contribution of other factors involved in altered distribution becomes more important. At 105 minutes after subcutaneous injection, brain levels of PCP in food-deprived rats were still elevated 30% over those of free-feeding rats given the same relative dose of the drug. This indicates that the reduced fat content in food-deprived animals may have reduced the importance of adipose tissue as a sink for the drug, i.e., its ability to divert the drug from sites of action in the brain and elsewhere. Reduction in hepatic drug metabolizing activity as a consequence of chronic food restriction may also have occurred in these rats.

It should be noted that for PCP abusers, dosage is probably not adjusted for body weight as it is in the laboratory; drugs are taken on a per-tablet or "hit" basis. The dose of 0.43 mg PCP/kg given

TABLE 3

PLASMA CORTICOSTERONE LEVELS IN FREE-FEEDING AND FOOD-DEPRIVED RATS AFTER PHENCYCLIDINE

	Dose of Phencyclidine HCl (mg/kg)			
	0	0.3	0.43	0.9
Free-feeding	29.8 ± 2.9	16.6 ± 3.7*	—	28.0 ± 4.0
Food-deprived	30.7 ± 4.8	33.4 ± 5.2‡	38.1 ± 3.9‡	46.9 ± 7.7*†

Values indicate plasma corticosterone levels (mg/100 ml; mean ± SE) in rats 105 minutes after PCP administration (n = 6, except for free-feeding 0.9 mg/kg group, where n = 7).

*Significantly different from corresponding saline group, $p<0.05$; Duncan's New Multiple Range test.

†Significantly different from low dose, $p<0.05$; Duncan's New Multiple Range test.

‡Statistically different from free-feeding 0.3 mg/kg dose level, $p<0.05$; Student's *t*-statistic.

to the 70% deprivation cohort was equivalent to the same absolute dose (on a milligram basis) as the 0.3 mg/kg dose delivered to free-feeding animals, yet yielded 186% of the brain concentrations. Therefore, unanticipated adverse reactions seen in street use of PCP could, in part, result from this dramatic difference in drug concentration at sites of action in persons of greatly differing physique, taking similar quantities of drug in the same social setting.

Despite 30% higher concentration of PCP in the brains of food-deprived rats, there were no dramatic differences detected in their unconditioned behavioral response to these doses of the drug, with the possible exception of the interaction of food deprivation with PCP to retard adaptation (as measured by the decline in lever touches with time). Retarded adaptation has been suggested to be the behavioral mechanism by which PCP elevates spontaneous motor activity (6) and might reflect PCP's disruptive effects upon learning, generally (3).

Woolverton, Martin and Balster (15) were able to demonstrate clear increases of PCP action in food-deprived rats only at doses of 4 mg/kg and greater. Lack of differences at the 1 and 2 mg/kg doses they tested could be ascribed to the relative insensitivity of their behavioral assay (no effects were clearly seen at these doses), but here, where a dose lower than 0.5 mg/kg produced a behavioral response, no alteration due to food deprivation was apparent.

In this experiment, corticosterone levels were probably elevated to an extent in the saline-treated animals because of handling and exposure to the novel environment during the experimental procedure. We expected PCP to elevate glucocorticoid levels even more in deprived animals, and this was observed. The reduction in plasma corticosterone levels, observed after the low dose of PCP in free-feeding rats, might reflect a tranquilizing action of this dose in these animals. What is more important is that PCP in dose ranges of 0.3 to 0.9 mg/kg in the food-deprivation groups led to a different corticosterone response from that in nondeprived groups. Corticosterone levels were 36% higher in the food-deprived 0.43 mg PCP/kg group than in free-feeding animals given 0.9 mg PCP/kg, while brain concentrations of drug in the latter group were 64% higher than those in the food-deprived animals given 0.43 mg PCP/kg. The results suggest a greater sensitivity of the adrenocortical system in food-deprived states, for which dispositional factors alone cannot account. It is probable that the deprivation manipulation acted to reduce adipose, so as to alter the disposition and, in addition, might have altered the rats' responsiveness to PCP because of the stressful consequences of both the deprivation procedure and exposure to a psychotropic drug having "tranquilizing" actions at low doses and sympathomimetic (stressful?) actions at higher doses. These complex interactions should be taken into account when studying the pharmacological effects of such agents.

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